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Archives OF INTERNAL MEDICINE

MARCH 1956
VOLUME 97 NUMBER 3

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John Louis, Louis R. Limarzi, and William R. Best, Chicago

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Subacute Bacterial Endocarditis

Carolyn J. Lingeman, Edward B. Smith, J. S. Battersby, and Roy H. Behnke, Indianapolis

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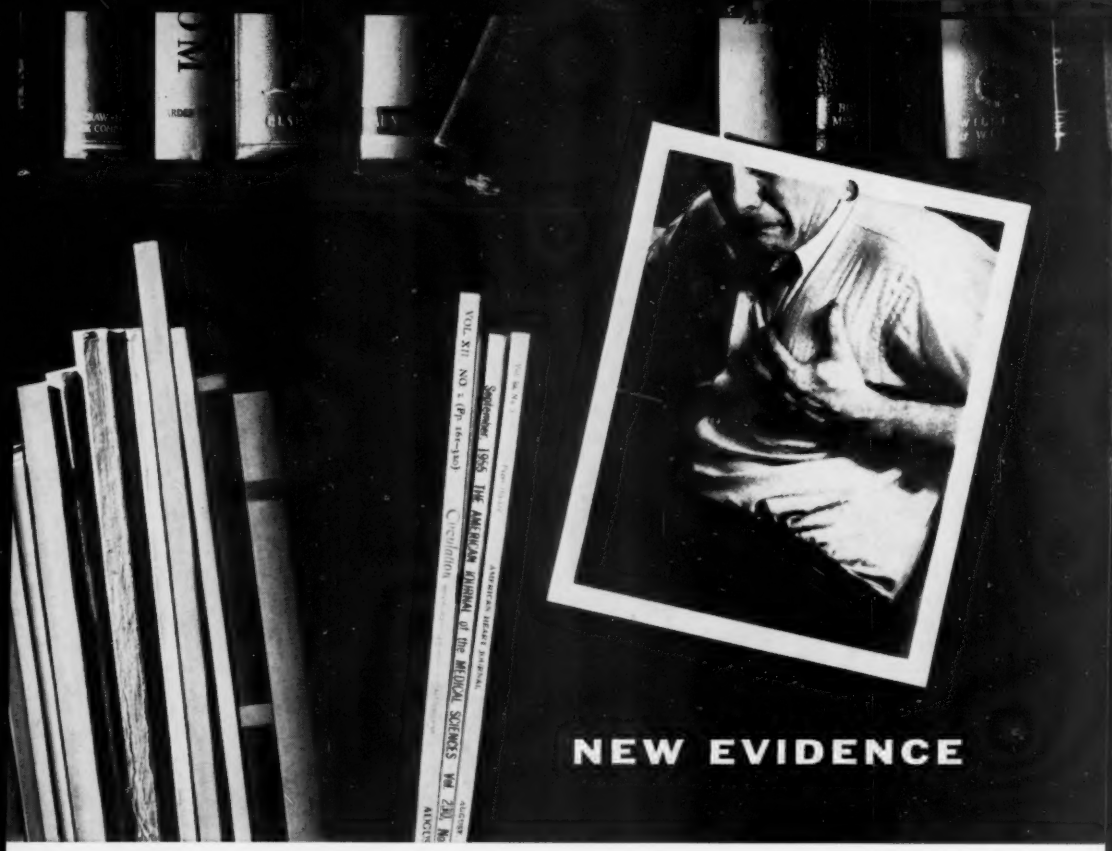

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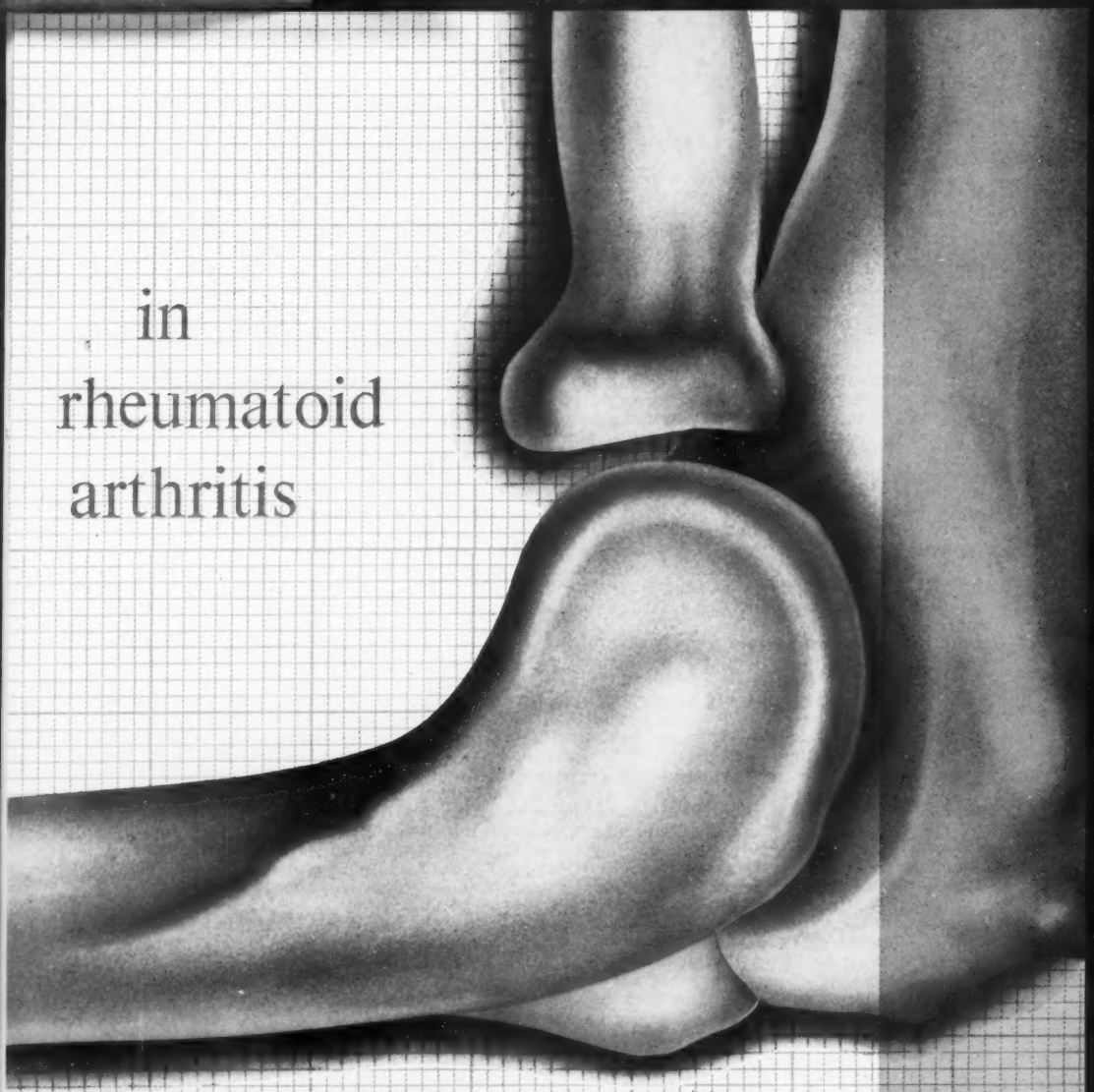

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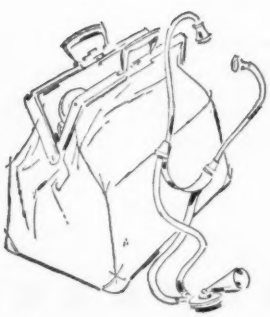

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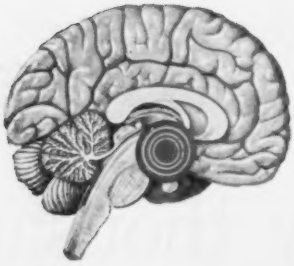

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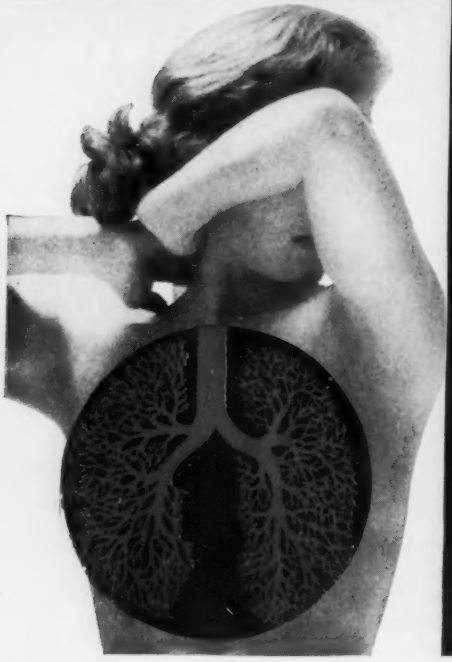

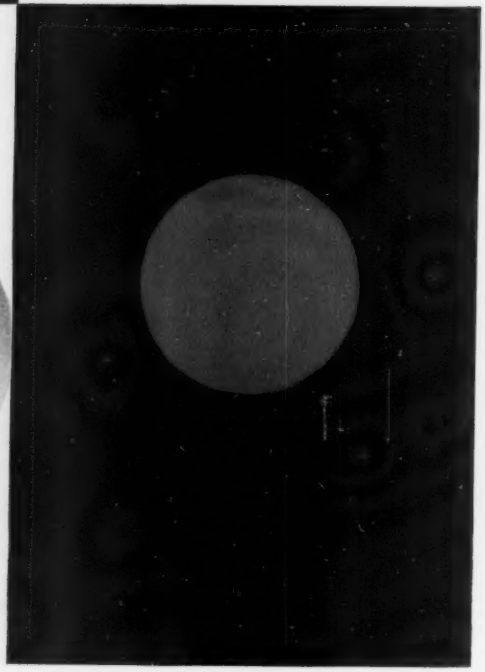

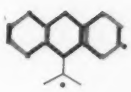

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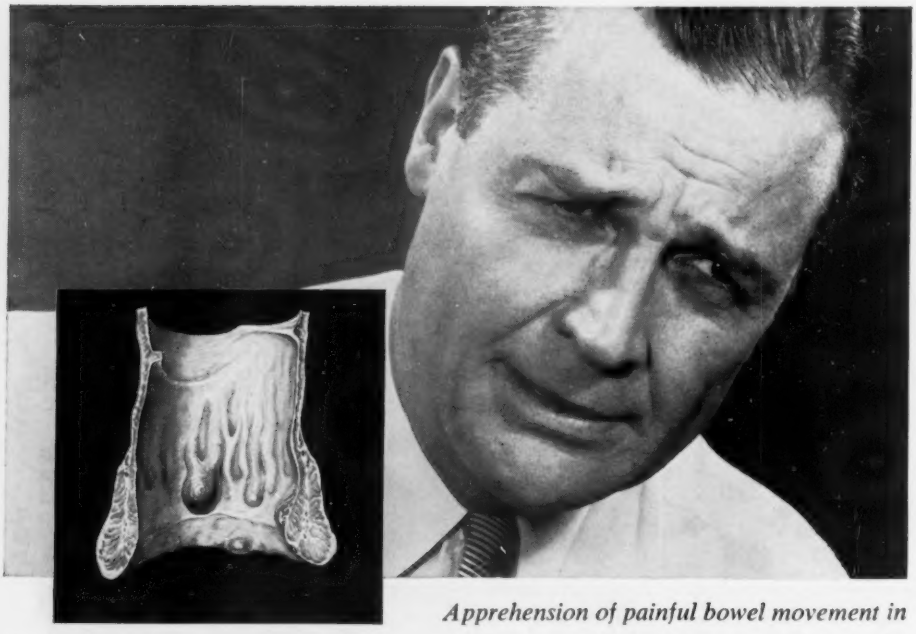

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*Soper, H. W.: Diseases of the Rectum and Colon: Their Diagnosis and Treatment, Am. J. Proctol. 4:113 (June) 1953.

SEARLE

Editorials

PROGNOSIS

ALTHOUGH prognosis—that branch of medicine which deals with the prediction of the course and outcome of disease—is tacitly recognized as being of the greatest importance, little has been written in the way of systematic analysis of the subject. And yet prognosis—outlook—is often the first thing about which the family and the patient inquire. What are his chances? How long will he be sick? In what sort of shape will he be left? are questions which the doctor is called on every day to answer. The older physicians spoke of prognosis *quoad vitam* and prognosis *quoad sanationem*. The first referred to death or survival. The second concerned health; in other words, even if the patient lives how long will he be ill, what will be the character of the course of the disease, and in what sort of condition will he emerge from his illness? These very terms indicate that prognosis is an analytical process.

Prognosis is based on past experience; large accumulations of statistics, individual experience, and laboratory tests are the essential facts. Prognosis can never be completely accurate, because there will always be the unforeseen or the accidental. However, like the predictions of the weather bureau, there it at least a sound underlying basis. It seems of interest, therefore, to break down the various classes of data on which prognosis is based; they fall into five groups.

A. First there are the gross statistical facts of a disease. Thus one knows in a general way that the outlook with abdominal cancer is bad, whereas with basal-cell epithelioma of the skin it is quite good. Rabies is notably fatal after symptoms set in, whereas practically no one ever dies of mumps. Meningioma is well known to have a better outlook than glioblastoma. One could multiply examples indefinitely.

B. Next to be considered are special conditions in the patient which have been found to be statistically important. Here one deals with such matters as age, sex, race, habits, etc. Given, for example, two patients with an equal degree of hypertension, obesity in one of them would be regarded as an adverse factor. Tuberculosis in general has a worse outlook in the Negro race than in whites. Of two patients with chronic hepatitis the one who insists on a heavy intake of alcohol would on the whole impair his chances for the future. Typhoid fever is well known to be a benign disease in children whereas it is much more serious in old people.

C. Next we come to special features of the indivdual case; here we deal with minutiae to which clinical experience has given importance, and many examples could be given of some special circumstance in a patient which apart from the general statistics of his disease will modify the outlook for the worse. Shock in coronary occlusion, anuria in the course of "lower nephron nephrosis," an enterococcus instead of an S. viridans in bacterial endocarditis immediately force on the physician a more guarded prognosis. These data are highly individualized and are usually gathered at the bedside.

D. Amenability of a disease to therapy is of course of the utmost importance in prognosis. The alteration in outlook of pneumococcal pneumonia after penicillin came into use, the discovery of insulin for diabetes, of liver for pernicious anemia

Submitted for publication Jan. 10, 1956.

are obvious examples. With cancer the presence of untreatable metastases immediately alters prognosis, as does, let us say, with a Staphylococcus bacteremia the discovery that the organism is resistant to the available antibiotics.

E. Finally, the possiblity of an unexpected accident must be taken into account in making a prognosis. Every careful physician will be guarded in his predictions during the first few weeks after a coronary occlusion no matter how well the patient "looks," because of the possibility of sudden ventricular tachycardia or other serious arrhythmia, embolus, or rupture. In the days when saccular aneurysm was frequent one never knew when rupture might occur. In a patient with "malignant" hypertension the outlook must always be qualified by the possibility of a sudden vascular accident.

When the experienced physician looks at a patient and quickly announces "he will recover," his pronouncement is actually based on a consideration of all of the above factors; only, with experience the analytical process may become lightning fast and indeed may be largely carried on subconsciously. The young doctor, however, may well profit by deliberately taking into account the various factors in prognosis which have been mentioned and by making a conscious analysis of the situation in the case of his patients. Such a running of mental scales will help develop later virtuosity.

A. L. Bloomfield, M.D.

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INTRODUCTION

Evaluation of the role of the adrenal cortex in the response of man to stressful situations continues to be a problem of major interest to medical investigators. Earlier studies suggested that the adrenal cortex responds actively and promptly to many, but not all, psychic and physical stresses.[1] In many of the studies, changes in the level of circulating lymphocytes or eosinophiles and

in the urinary excretion of 17-ketosteroids were employed as indicators of adrenal cortical activation. It is well appreciated that these indices are not specific indicators of adrenal cortical activation. For example, it is known that epinephrine is capable of inducing a decrease in circulating eosinophiles in the absence of functioning adrenal cortical tissue [2] and that the urinary excretion of 17-ketosteroids in males reflects testicular, as well as adrenocortical, secretory products. It appeared worth while, therefore, to investigate further the response of the adrenal cortex to stress, employing techniques which measure adrenal cortical activation more directly.[3] In addition, it appeared highly desirable to analyze further the relative importance of physical and psychological factors as activators of adrenal cortical function. To this end a group of endocrine-metabolic investigators collaborated with a team of psychologists and psychiatrists in a joint and expanded study of a stress situation to which both groups had devoted considerable time and effort in previous years.

An earlier study of a college crew during a four-mile race suggested, on the basis of changes in the circulating eosinophile count, that the physical and emotional tension incident to the race was sufficient to produce increased adrenal cortical activity.[4] Whether the eosinopenia observed in this study reflected predominantly adrenal cortical or adrenal medullary response could not be determined conclusively with the techniques employed at that time.

It was hoped that in the present study of a college crew under similar circumstances the measurement of changes in total urinary 17-hydroxycorticoid excretion by a technique recently devised [3] might provide a practical method of obtaining a partial answer to this question. Earlier studies on normal subjects had indicated that a quantitative relationship exists between the percentage fall in circulating eosinophiles and the rise in total 17-hydroxycorticoid material in the urine in response to a four-hour period of corticotropin (ACTH) administration.[1] Under these specific circumstances a fall in circulating eosinophiles of 40% to 50% was characteristically accompanied by an increase of approximately 0.5 to 1.0 mg. in total urinary hydroxycorticoid material during the four-hour period immediately following corticotropin administration. Thus, an eosinopenia observed under stress without an accompanying increase in urinary 17-hydroxycorticoid excretion might (1) reflect an eosinopenia mediated by extra-adrenocortical factors, such as epinephrine, or (2) indicate altered metabolism of adrenal steroids following a standard secretory response or (3) result from varying combinations of both reactions. Obviously, a definitive answer to this problem must await the development of satisfactory methods for the determination of the principal metabolic products of both cortical and medullary hormones in blood and urine.

In the earlier study of college oarsmen it was observed that the eosinophile levels of the coxswain and the coach also fell during the race.[4] This indicated quite clearly that the physical exertion of rowing was not the only stress involved capable of inducing a marked eosinopenia. From these observations, it appeared essential to include psychological observations in an effort to correlate the relation between the emotional make-up and biological response of the several crew members. For this purpose, an interview with a psychiatrist, Rorschach tests, and Thematic Apperception Tests were integrated with the clinical and metabolic observations.

Because changes in uropepsin excretion have been observed under stress and because of the known relationship between uropepsin excretion and adrenal cortical activity,[5] determinations of urinary uropepsin excretion also were carried out in the 1954 studies.

The studies on the crew have been supplemented by other experiments designed to elucidate further (1) the relative importance of physical exercise and psychological stimulation as adrenal cortical activators and (2) mechanisms which might modify the intermediary metabolism and excretion of adrenal

cortical steroids. Adrenal steroid excretion and changes in the level of circulating eosinophiles were followed in normal subjects participating in other forms of athletics. Also investigated were the effects of exercise on four patients with Addison's disease receiving a constant infusion of glucocorticoids. One patient with bilateral adrenal cortical hyperplasia who performed a standardized exercise test was also studied. Because of the large weight losses (3 to 4 kg.) observed in the crew members during the course of a four-mile race, an analysis of the possible loss of 17-hydroxycorticoids in sweat was undertaken.[6]

To gain insight into the metabolic response of normal subjects undergoing psychological stimulation, studies were made on medical students during the second-year final examinations and on fourth-year students who were presenting a case for the first time before the assembled senior staff of the hospital. Candidates for the Ph.D. degree were also studied during the period of their general examinations, and a mixed professional group was observed during the showing of a documentary film of primitive tribal rites designed to elicit an intense emotional response.

METHODS

Metabolic Methods

As in the previous study,[4] the subjects were college crew members observed during the final two weeks of intensive preparation for an intercollegiate race, the finale of the rowing season. The study was restricted to the eight oarsmen of the 1953 and 1954 crews and their coxswains; three persons, Nos. 3, 5, and 8, were common to both the 1953 and the 1954 crews. The 1954 varsity crew manager was also studied.

The 1953 crew members ranged in age from 19 to 21 and in weight from 168 to 193 lb., except for the coxswain, who weighed 126 lb. All were in excellent health at the time of the study. Only one man (No. 3) presented a history of allergy (seasonal hay fever). However, he showed no appreciable eosinophilia. The 1954 crew members ranged in age from 19 to 21 and in weight from 170 to 198 lb., except for the coxswain, who weighed 135 lb. All were in excellent health. Two men had a history of allergy: i. e., No. 6 gave a history of seasonal hay fever and No. 10 had nonspecific skin allergies. Both persons exhibited some degree of eosinophilia.

In 1953 and in 1954 the crews followed a similar schedule and were studied in the same environment. During the two weeks preceding the race, the crew members lived a comparatively isolated existence in special training quarters. Food was plentiful, and rest was ample; distractions were minimized and visitors prohibited. The varsity crew lived and ate apart from the members of other crews, i. e., junior varsity and freshman crews. There was complete devotion to the task of training for the race. Except for Sundays, when there was no rowing, each day included two periods of practice rowing of one to two hours each, in the morning between the hours of 7:00 a. m. and 8:30 a. m. and in the late afternooon between 5:30 p. m. and 7:30 p. m. Other than this, only light exercise was allowed. Three time trials, in which the four-mile race course was covered at racing speed, were held each year in place of one of the regular afternoon practice sessions. The last time trial took place one week before the varsity race. The time required to cover the four-mile course at racing speed was usually 20 to 23 minutes. The physical exertion expended in the time trials was entirely comparable to that expended during the varsity race. The intercollegiate varsity race took place at approximately the same time as the afternoon practice sessions. In 1953 it was apparent from the beginning of the race that the crew under study would probably win. This was much different from the experience in 1954, in which the outcome was very doubtful throughout the entire race. The race was won in 1953 and lost in 1954. In 1953, the membership of the varsity crew was stable throughout the two-week training period, whereas in 1954 three substitutions (Nos. 2, 3, and 7) were made approximately 10 days before the race.

Eosinophile counts were taken on the 1953 crew at approximately 5 p. m. and 9 p. m. on the following days: two Sundays on which there was no rowing, one day of regular practice, two time-trial days on which the race course was covered at racing speeds, and on the day of the varsity race. An attempt was made to obtain the final eosinphile count two to four hours after exercise, and for this reason the late evening counts were occasionally carried out at 10 or even 11 p. m. In 1954, eosinophile counts were done at 9 a. m., just after the morning practice period, as well as at 5 p. m. and 9 p. m. on control, practice, time-trial, and race days. Capillary blood samples were obtained for eosinophile counts from the ear lobes and were stained with phloxine B-propylene glycol stain, as previously reported.[7] One white blood cell pipette was filled and two to four chambers were counted for each determination. At the level of eosinophiles encountered in most of the subjects,

a reduction of greater than 40% is considered significant.[8]

In 1953, urine specimens were collected on one Sunday, a time-trial day, and the race day. Urine was collected from 9 a. m. to 1 p. m., 1 p. m. to 5 p. m., 5 p. m. to 9 p. m., and overnight (except that no 9 a. m. to 1 p. m. specimen was obtained on the time-trial day); these times are approximate (Table 3). The specimens were measured; a few drops of toluene were added as a preservative, and an aliquot was stored at refrigerator temperature. Within two weeks, creatinine and 17-hydroxycorticoid determinations were carried out on these specimens.

In 1954, specimens were collected from 9 a. m. to 1 p. m., 1 p. m. to 5 p. m., 5 p. m. to 9 p. m., and 9 p. m. to 9 a. m. on a Sunday, a regular practice day, a time-trial day, and the race day. The specimens were measured, and an aliquot was stored, as with the 1953 specimens, except that no preservative was added. Determination of 17-hydroxycorticoid, 17-ketosteroid, uropepsin, and creatinine excretion was performed on each specimen.

Estimation of total urinary 17-hydroxycorticoids was done by a method previously described.[3] Normal values for this method range from 1 to 10 mg. per 24 hours for young men. Results are expressed as milligrams of corticoid excreted per four hours and represent averages of duplicate determinations.

The urinary 17-ketosteroids were determined by a modification of the method of Drekter and coworkers,[9] whereby the colorimetry was performed as in the procedure of Holtorff and Koch.[10] Normal values range from 14 to 25 mg. per 24 hours for young men. In the present study the results are expressed as milligrams per four hours.

Uropepsin was determined by a modification[5] of the methods described by Bucher and by Anson and Mirsky.* Results are reported in terms of units per four hours. The range of normal values for this determination in 120 hospitalized patients without demonstrable gastrointestinal disease is 1200 to 3800 units per 24 hours. Recent unpublished data, however, suggest that higher values may be anticipated in normal young males under the common stress of college work.†

Creatinine excretion was measured by Folin's method, as modified by Lambert.[13] Results are expressed as milligrams per 24 hours.

To minimize the effect of minor inaccuracies in the timing of urine collections, the values for each subject were corrected according to the average creatinine content of all his specimens. In every case, however, the corrections were insignificant. In two instances in 1954 (5 to 9 p. m. specimens on race day, Subjects 2 and 9) in which the creatinine value was obviously so low as to indicate grossly faulty collection, the values were discarded, and in the statistical analysis these values were calculated by the method of fitting constants.

Statistical Methods

Although this study was not designed primarily for statistical analysis, on review of the data such an analysis appeared justified in an attempt to direct future studies and to define more precisely the limitations of the data obtained.

Statistical comparisons of the 1953 data were made by Students' "*t*" test, and values for *P* were obtained from the standard tables of Fisher.

A split-plot analysis of variance[14] was carried out on the 1954 17-hydroxycorticoid, 17-ketosteroid, and uropepsin determinations, with use of three periods (9 a. m. to 1 p. m., 1 to 5 p. m., and 5 to 9 p. m.) and three days (control, practice, race), in which individual subjects were considered main plots and days were considered as the treatments applied to the main plots. The differences between periods and the day-by-period interactions were considered as treatments applied to the subplots.

In the analysis of variance on the 17-hydroxycorticoids, it was suspected that the error term was heterogeneous, and therefore separate analyses of variance by individual subjects were made. It was found by Bartlett's test that the suspected heteroscedasticity was present. This is interpreted as meaning that the individual members of the crew varied significantly ($0.03 > P > 0.01$) with respect to the change in trend of 17-hydroxycorticoid output on race day as compared with the control and practice days.

Further, a multiple correlation analysis[15] was carried out between the 17-hydroxycorticoids, 17-ketosteroids, and uropepsin determinations on both the total and individual data for 1954. Ninety-five per cent confidence limits were calculated for the total data.

Psychologic Methods

Psychologic methods of observations were selected which could elucidate the characteristic pattern of each person's response to life stress, his motivations for varsity rowing, and the nature of his identification with the crew as a group.

Psychological studies of the 1953 crew included only a group Rorschach test.‡ This procedure provides a rapid method for the estimation of

* References 11 and 12.

† Gray, S. J., and Krakauer, L. J.: Unpublished data.

‡ References 16 and 17.

each person's emotional drives and energies as well as his characteristic way of responding to them. The group Rorschach, which was administered a week before the race, seemed appropriate and acceptable, since the crew members were living, as well as rowing, together. Although this procedure illuminated the variety of personality differences among the various men, the Rorschach test could not give information concerning the significance of rowing and of the race to the individual members of the crew. Psychological study of the 1954 crew included a repetition of the group Rorschach test, an individual Thematic Apperception Test (TAT),[18] and a personal interview conducted by an experienced psychiatrist.

In the 1953 study the psychologist was introduced to the crew one evening after the men had finished dinner in their private dining room at training headquarters. Instead of watching a movie, the men were asked to take a personality test. They were handed several sets of Rorschach psychodiagnostic plates. Each set included ten ink blots, five colored and five black and gray. The men were asked to look at each card for two minutes, during which they were asked to write down anything they saw in the ink blot or anything the blot suggested. This procedure took approximately 20 minutes. The men were then asked to circle a blot on a facsimile of the test card in order to indicate how much of the blot was included in the response. They were also asked to indicate what it was about the card that had helped them to see what they described. Their attention was called to the fact that form, movement, color, or shading might have been a leading determinant for each object perceived. In other words, the men were invited to assist in the preliminary classification of their responses. In the 1954 study, the Rorschach test was administered to the crew in a similar fashion six weeks before the race. It was then repeated one week prior to the race in order to determine whether the imminence of the race as well as the intensive training program had affected the psychological response to the test. Because of late substitutions in the crew line-up, only seven men were tested on both occasions.

In 1954, approximately six weeks before the race the physician responsible for the medical care of the crew asked the men to cooperate in a research study in which an attempt would be made to determine whether there might be any relationship between a person's background and temperament and the nature of his physiological response as measured by a biochemical study of urine collected at certain intervals. A personal interview with the psychologist and also with the psychiatrist was scheduled for each man. The psychiatrist explained that the interview was tape-recorded but that personal information would be regarded as confidential. During the hour interview, each man was encouraged to tell as much as he could about how he happened to come to this university and try out for crew. When information was given concerning the family background, interest was shown in order to obtain comments about relationships to parents and siblings. The men were glad to describe their experiences on the crew, and many of them gave vivid accounts of how it feels to row in a race.

Individual Thematic Apperception Tests were carried out by the psychologist on the same evening. Because of late changes in the composition of the crew, the three new members were interviewed and tested at training headquarters one week before the race. As with the Rorschach test, the TAT cards invite the subject to express feelings and phantasies with relative freedom from the personal censorship which often guards response to direct questioning. The Thematic Apperception Test consists of pictures representing situations which can be perceived as emotionally charged situations or events. Ten cards were used, the subject being asked to create a dramatic story for each picture. He was given five minutes to elaborate each card. The cards included pictures designed to bring out information about the meaning to each man of racing with the crew. One card, for instance, depicted four men lying on the grass. Special attention was paid to whether the subject perceived this as a unified group or as four separate persons, whether the group was perceived as quarreling or cooperating, as successful or unsuccessful. Another card represented a half-naked man climbing a rope. This card is frequently interpreted as an escape theme or as an athletic exercise. When shown this card, subjects often express feelings about athletic participation, commenting on bodily strength or weakness.

The psychologist and the psychiatrist each reviewed and summarized his data independently. Joint meetings were then devoted to combining the psychological observations into a series of individual portraits, each comprising the responses to the Rorschach test and Thematic Apperception Test as well as the most illuminating statements the man made concerning his family relationships, personal drives and ideals, feelings about rowing, and attitude about the crew as a group. The psychological interpretations were completed previous to correlation with the metabolic changes.

METABOLIC OBSERVATIONS

Changes in Eosinophile Level § (Tables 1 and 2)

A. Initial Control Level.—The initial control levels of circulating eosinophiles revealed no abnormalities except for the slight eosino-

§ Changes in eosinophile level refer to changes in the value of the mean unless otherwise stated.

TABLE 1.—*Blood Eosinophile Response in College Oarsmen (1953 Crew)*

	Control, No Rowing						Practice Rowing			Time Trial						Race Day		
	5/31/53			6/7/53			6/2/53			6/3/53			6/6/53					
	Eos./Cu. Mm.			Eos./Cu. Mm.			Eos./Cu. Mm.			Eos./Cu. Mm.			Eos./Cu. Mm.			Eos./Cu. Mm.		
Subject	5 P. M.	9 P. M.	% Change	5 P. M.	9 P. M.	% Change	5 P. M.	9 P. M.	% Change	5 P. M.	9 P. M.	% Change	6 P. M.	10:30 P. M.	% Change	5:30 P. M.	11:30 P. M.	% Change
1	141	206	+46	133	131	—2	144	50	—65	147	34	—77	141	50	—64	106	25	—76
2	101	56	—45	126	94	—25	56	..	....	94	25	—73	134	113	—16	87	22	—75
3	81	84	+4	200	244	+22	100	25	—75	75	62	—17	87	113	+30	156	25	—84
4	194	...	....	168	151	—10	132	37	—72	106	28	—74	144	56	—61	131	19	—86
5	172	144	—16	250	178	—29	44	69	+57	160	125	—22	156	93	—40	100	25	—75
6	131	84	—36	131	131	0	117	12	—90	75	20	—73	75	50	—33	56	8	—86
7	131	125	—5	131	94	—28	75	9	—85	117	16	—86	100	33	—66	69	12	—83
8	175	213	+22	200	187	—6	175	62	—65	117	72	—38	156	106	—32	78	16	—79
9 (Cox)	138	144	+4	100	178	+78	269	119	—56	106	132	+24	150	106	—29	69	31	—55
Range	81-194	56-213	—45-+46	100-250	94-244	—31-+78	44-269	9-119	—90-+57	75-160	16-132	—86-+24	75-156	33-113	—66-+30	56-156	8-31	—86—55
Mean	140	132	—3	159	154	0	123	48	—57	111	57	—48	127	80	—35	95	20	—78
S. E.	12	20	10	16	16	11	23	13	17	10	15	12	10	11	10	11	2	10

TABLE 2.—*Blood Eosinophile Response in College Oarsmen (1954 Crew)*

	Control, No Rowing (6/13/54)					Practice Rowing (6/12/54)				Time Trial (6/11/54)				Race Day (6/19/54)				
	Eos./Cu. Mm.			% Change		Eos./Cu. Mm.			% Change	Eos./Cu. Mm.			% Change	Eos./Cu. Mm.			% Change	
Subject	9 A. M.	5 P. M.	9 P. M.	9-5	5-9	9 A. M.	5 P. M.	9 P. M.	5-9	9 A. M.	5 P. M.	9 P. M.	5-9	9 A. M.	5 P. M.	9 P. M.	9-5	5-9
1	119	106	188	—11	+77	60	206	100	—51	75	106	47	—56	106	78	19	—26	—76
2	63	94	106	+49	+13	50	206	37	—82	63	106	6	—94	126	63	6	—50	—90
3	103	125	125	+21	0	50	131	56	—57	53	106	28	—74	120	125	34	+4	—73
4	60	72	94	+20	+31	47	75	44	—41	62	108	16	—85	63	78	12	+24	—85
5	166	177	175	+7	—1	100	114	112	—2	69	131	41	—69	163	125	47	—23	—62
6	256	275	356	+7	+29	206	273	275	+1	196	396	47	—88	416	298	62	—28	—79
7	75	95	63	+27	—34	38	112	100	—11	75	69	13	—81	88	78	25	—11	—68
8	91	94	144	+3	+53	92	112	62	—45	44	131	40	—69	106	50	25	—51	—50
9 (Cox)	178	155	188	—13	+21	92	162	187	+15	140	229	181	—21	225	144	78	—36	—46
Range	60-256	72-275	63-356	—13-+49	—34-+77	38-206	75-273	37-275	—82-+15	44-196	69-396	6-181	—94—21	63-416	50-298	6-78	—51-+24	—90—46
Mean	123	138	160	+12	+21	82	155	108	—30	86	154	47	—71	157	115	34	—22	—70
S. E.	22	21	28	6	11	17	21	26	11	16	34	18	7	36	25	8	8	5
10 (Mgr.)	...	...	...	....	....	...	...	...	....	276	284	300	+6	409	266	313	—35	+18

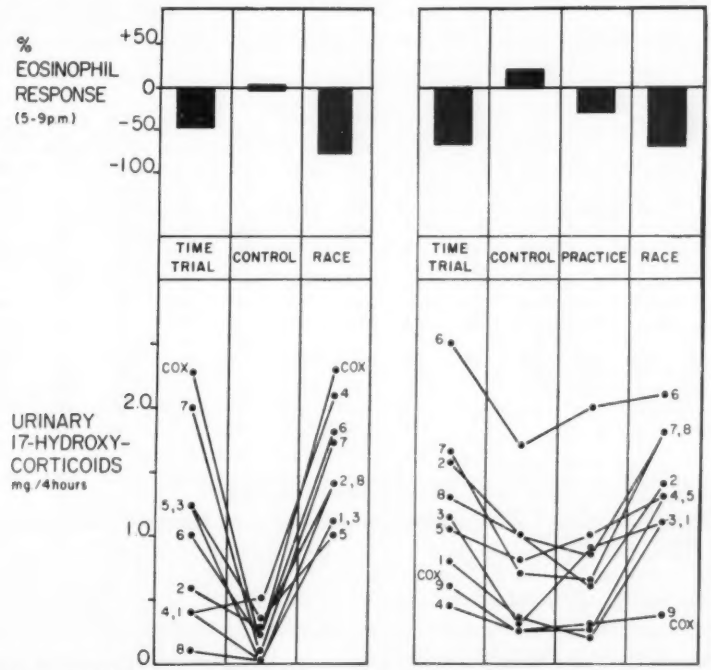

Fig. 1.—Circulating eosinophiles and urinary 17-hydroxycorticoid excretion in the crews of 1953 and 1954. The first three columns are the crew of 1953, and the last four columns are the crew of 1954. The urinary 17-hydroxycorticoid response illustrated represents that amount of corticoid material obtained in the 5 to 9 p. m. individual specimens.

philia (200 to 400 cells per cubic centimeter) exhibited by two members of the 1954 crew (Nos. 6 and 10) (Table 2).

B. Changes in Eosinophile Level Between 5 P. M. and 9 P. M. (Fig. 1).—1. Control Days: In 1953 and in 1954 the change in the level of eosinophiles between 5 p. m. and 9 p. m. was studied. In 1953 the change during this period was negligible on the two control days which were investigated. In

TABLE 3.—*Urinary 17-Hydroxycorticoid Excretion in College Oarsmen (1953 Crew)*

	Control, No Rowing (6/7/53)					Time Trial (6:30-7 P. M., 6/3/53)			Race Day (Race 7:45-8:05 P. M., 6/12/53)				
Subject	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	1 P. M. to 5 P. M.	5 P. M. 9:30 P. M.*	9:30 P. M. 6:30 A. M.*	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.	Total Day
1	1.2	1.2	<0.1†	<0.3	3.4	<0.2	0.4	1.8	<0.2	1.6	1.1	<0.3	3.8
2	1.8	2.8	0.3	0.7	7.0	1.4	0.6	0.4	1.3	2.7	1.4	0.5	6.9
3	0.9	0.7	<0.1	<0.3	2.6	3.6	1.2	2.4	<0.1	<0.4	1.1	1.2	5.2
4	1.8	0.5	0.5	<0.1	3.1	0.4	0.4	1.5	1.8	1.2	2.1	1.8	10.5
5	1.5	0.1	<0.3	<0.5	3.4	0.7	1.2	<0.2	<0.2	1.1	1.0	1.0	5.3
6	2.1	0.9	0.2	<0.3	4.1	1.4	1.0	0.8	1.2	2.0	1.8	1.6	9.8
7	...	3.3	<0.2	<0.2	...	0.6	2.0	1.5	3.0	4.0	1.7	...	...
8	2.0	1.2	<0.1	<0.4	4.5	2.2	<0.2	<0.4	1.0	2.2	1.4	1.8	10.0
9	1.8	1.5	0.2	<0.2	4.1	1.5	2.3	0.4	2.9	2.6	2.3	3.2	17.4
(Cox)													
Range	0.9-2.1	0.1-3.3	<0.1-0.5	<0.1-0.7	2.6-7.0	<0.2-3.6	<0.2-2.3	<0.2-2.4	<0.1-3.0	<0.4-4.0	1.0-2.3	<0.3-3.2	3.8-17.4
Mean	1.6	1.4	0.2	0.2	4.0	1.3	1.0	1.0	1.3	2.0	1.5	1.4	8.6
S. E.	0.1	0.3	0.04	0.06	0.5	0.4	0.2	0.3	0.4	0.4	0.02	0.3	1.5

* All values, except those for total day, represent milligrams of corticoid per four hours, corrected according to creatinine excretion.

† When specimens contain less than 1 mg. of corticoid per liter, the content is recorded as less than (<) the amount calculated on the basis of 1 mg. per liter.

TABLE 4.—*Urinary 17-Hydroxycorticoid*

	Control, No Rowing										Practice Rowing					
	6/6/54					6/13/54					6/12/54					
Subject	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day†	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 P. M. to 9 A. M.*
1	0.9	<0.4‡	<0.4	<0.4	2.9	0.8	<0.3	<0.3	<0.2	2.0	0.8	0.8	<0.2	<0.3	2.6	...
2	...	...	...	...	...	1.7	1.8	1.0	0.7	6.7	1.4	1.2	1.0	1.1	7.0	1.3
3	0.5	0.5	0.3	<0.4	2.6	1.2	0.4	0.4	<0.2	2.6	0.8	0.5	0.9	0.7	4.3	0.8
4	0.8	1.0	<0.2	0.6	4.0	2.1	1.0	0.4	0.4	4.6	0.8	0.5	0.6	0.4	3.0	0.2
5	1.9	1.3	0.8	1.4	8.2	1.7	1.3	0.8	1.5	8.4	1.2	1.2	1.0	0.6	5.1	1.4
6	2.3	1.9	1.4	1.0	8.6	2.5	2.2	1.7	0.7	8.4	2.1	2.3	2.0	1.9	12.2	1.5
7	...	...	...	...	...	1.6	1.2	0.7	0.8	6.0	1.3	1.2	0.6	1.0	5.9	1.4
8	1.3	1.3	1.0	1.0	6.5	1.5	0.8	1.0	0.9	6.0	1.4	0.7	1.2	0.6	5.1	1.7
9 (Cox)	0.3	<0.2	<0.3	<0.2	1.3	0.6	0.2	<0.2	0.3	1.9	0.8	0.5	0.3	0.3	2.6	0.2
Range	0.3-2.3	<0.2-1.9	<0.2-1.4	<0.2-1.4	1.3-8.6	0.6-2.5	0.2-2.2	<0.2-1.7	<0.2-1.5	1.9-8.4	0.8-2.1	0.5-2.3	<0.2-2.0	<0.3-1.9	2.6-12.2	0.2-1.7
Mean	1.1	0.9	0.6	0.7	4.9	1.5	1.0	0.7	0.6	5.2	1.2	1.0	0.9	0.8	5.3	1.0
S. E.	0.28	0.23	0.18	0.16	1.1	0.20	0.23	0.16	0.14	0.85	0.15	0.19	0.18	0.17	1.0	0.21
10 (Mgr.)	2.6	1.4	1.1	...	...	...	...	...	...	...	...	...	...	...	...	1.3

* All values, except those for total day, represent milligrams of 17-hydroxycorticoid per four hours, corrected according to creatinine excretion; the over night values are rounded to the nearest decimal point.
† Total day figures are sums of all actual values.
‡ When specimens contain less than 1 mg. of 17-hydroxycortocoid per liter, the content is recorded as less than (<) the amount calculated on the basis of 1 mg. per liter.
§ Calculated by the method of fitting constants.

1954 an increase of 20% was noted during this period, five of nine persons (1954) displaying an appreciable increase (Table 2). A slight increase in eosinophiles occurring late in the day is consistent with the diurnal variation known to occur in man.

2. Practice Day: The 1953 practice day consisted of an unusually severe workout, and a decrease of 57% was observed between 5 p. m. and 9 p. m.; eight of nine subjects experienced some fall in eosinophiles. In the ninth subject the initial eosinophile level of 44 per cubic millimeter was unusually low and undoubtedly was a major factor in minimizing further changes in this direction. During the 1954 practice day a smaller decrease was observed, i. e., an over-all fall of 30%. In this instance seven of nine subjects exhibited some degree of eosinopenia.

3. Time Trials: In 1953 a 48% and a 35% decrease in eosinophiles were observed between 5 p. m. and 9 p. m. on time-trial days. These changes were similar in direction and magnitude to those observed during the practice day, but they were less uniform. In contrast, the changes noted during the time trial in 1954, a decrease of 69%, corresponded more closely to the changes observed on the varsity-race day (a decrease of 70%) rather than to those of the practice day, on which a decrease of only 30% occurred.

4. Varsity-Race Day: The race day, in both 1953 and 1954, was marked by the lowest 5 p m. eosinophile count (? anticipation) found throughout the study, i. e., 95 (1953) and 115 (1954), as compared with control-day levels of 149 and 133, respectively. In 1954, on race day there was a decrease of 25% in eosinophiles during the period 9 a. m. to 5 p. m., in contrast with a 15% increase observed during a similar period on a control day (Sunday). In 1953 there was a subsequent fall of 78% during the race, with a decrease being noted in all oarsmen and the coxswain. In 1954 there was a decrease of 70% in which, again, all oarsmen and the coxswain participated. The response of the 1954 coxswain (No. 9) on both the time-trial and the race day was in the same direction as that of the eight oarsmen but was the smallest in magnitude. In 1954 the manager (No. 10) showed his lowest eosinophile level at 5 p. m., which was somewhat before the race. However, it is of some interest that this time corresponded well with the period of his maximum managerial responsibilities, which reached a peak in the eight-hour period prior to the race.

Excretion in College Oarsmen (1954 Crew)

6/15/54				Time Trial (6/11/54)					Race Day (6/19/54)						
9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M	Total Day	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 P. M. to 9 A. M.*	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day (6/18-19)	Total Day (6/19-20)
0.6	0.5	<0.3	...	1.0	1.6	0.8	0.6	5.2	0.5	0.6	1.2	1.1	...	4.5	...
1.0	0.8	0.6	6.4	1.2	1.4	1.6	1.7	9.3	1.5	1.6	1.4	1.4§	...	8.9	...
0.8	0.6	0.7	4.5	0.4	0.7	1.2	0.8	4.7	0.5	1.1	0.8	1.1	1.8	4.6	8.6
1.5	0.7	<0.2	3.1	1.4	2.2	0.5	...	...	0.6	2.0	1.1	1.3	...	6.1	...
0.4	0.7	1.0	6.2	0.6	1.4	1.0	1.4	7.3	1.2	1.2	1.5	1.3	2.4	7.5	11.3
2.0	2.0	1.5	10.1	2.7	2.0	2.5	1.9	13.0	1.8	2.5	2.5	2.1	...	12.5	...
1.6	0.6	0.7	7.0	1.1	1.8	1.6	0.8	7.0	1.2	1.8	1.5	1.8	...	8.8	...
1.9	0.8	0.8	8.4	1.4	1.6	1.3	1.1	7.6	1.4	1.6	2.9	1.8	2.5	10.6	13.7
0.6	0.7	<0.3	2.2	0.6	0.5	0.6	...	...	...	0.6	0.3	0.4§	...	...	...
0.4-2.0	0.5-2.0	<0.2-1.5	2.2-10.1	0.4-2.7	0.5-2.2	0.5-2.5	0.6-1.9	4.7-13.0	0.5-1.8	0.6-2.5	0.3-2.9	0.4-2.1	1.8-2.5	4.5-12.5	8.6-13.7
1.2	0.8	0.7	6.0	1.2	1.5	1.2	1.2	7.7	1.1	1.4	1.5	1.4	2.2	7.9	11.2
0.20	0.15	0.13	0.93	0.23	0.19	0.21	0.19	1.1	0.17	0.21	0.27	0.17	...	1.0	...
2.1	1.6	1.2	8.7	1.8	1.6	1.4	1.9	10.6	2.0	2.3	4.0	3.1	...	15.3	...

In summary, it was of interest to note that the usual diurnal rhythm of eosinophiles (a progressive increase in cell count during the afternoon and evening) was not observed on the control days in the 1953 crew studies; it was observed in 1954. The obliteration of the diurnal pattern is compatible with increased adrenal cortical or medullary secretory activity during this period, as compared with the usual finding of decreased activity in the afternoon and evening (diurnal rhythm). In 1953, the decrease in eosinophile levels during time trials closely resembled that seen during practice rowing, whereas in 1954 the change in eosinophile level on time-trial day more closely resembled that noted on race day. On race day in 1954 there was a progressive decrease in circulating eosinophiles from 9 a. m. to 5 p. m. and from 5 p. m. to 9 p. m. Unfortunately, similar observations were not made in 1953. The pre-race eosinophile level (5 p. m.) in both years was noteworthy in that it was the lowest level encountered at this time of day and presumably reflected an anticipatory response to the race. During the race in both years there was a profound eosinopenia, in which all crew men participated. The response of subject No. 9 (coxswain) in 1954 was less than that of any other subject in the two years under study.

Changes in Urinary Total 17-Hydroxycorticoid Excretion

Observations on the urinary 17-hydroxycorticoids, expressed as milligrams excreted per four hours, are presented in Tables 3 and 4 and are summarized in Figures 1, 2, 3, and 7.

A. Diurnal Variation in Total 17-Hydroxycorticoid Excretion.—1. Control and Practice Days: On both 1953 and 1954 control days the subjects as a group exhibited the expected diurnal pattern of corticoid excretion which the authors have observed in many subjects, i. e., a higher excretion during the morning and early afternoon than at night. In 1954 the progressive decrease in the day level is quite similar on both the control and practice days, there being no statistically significant difference between them (Fig. 2).

The control day 9 a. m. to 1 p. m. 17-hydroxycorticoid excretion was quantitatively similar in 1953 and 1954. The control day 5 to 9 p. m. and overnight values, contrariwise, were noticeably lower in 1953, i. e., 0.2 mg. as compared with 0.7 mg. (Fig. 3).

2. Control Day *vs.* Race Day: Comparison between the 1953 race day and control day disclosed no significant difference between values obtained in the 9 a. m. to 1 p. m. pre-race specimen; this was likewise true of

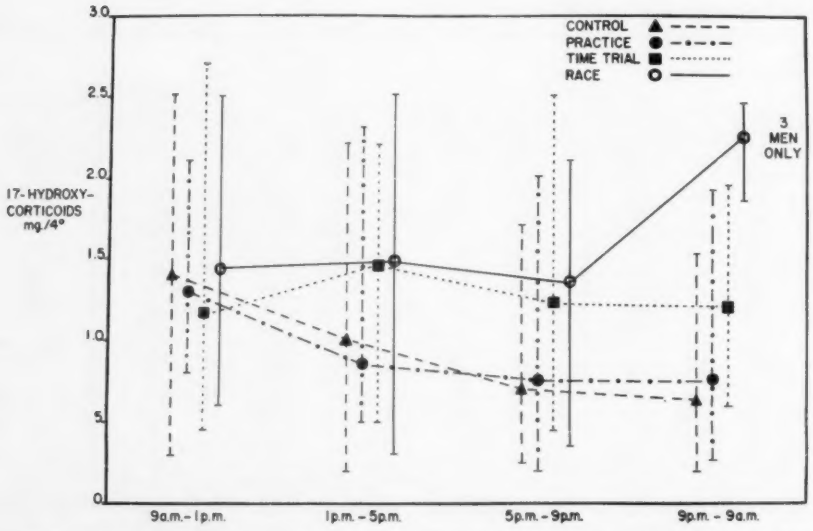

Fig. 2.—This figure represents the mean and range of the 17-hydroxycorticoid excretion of the eight oarsmen of the 1954 crew during the four periods studied. Since only three men collected 9 p. m.-9 a. m. specimens following the race, these values are not considered in the statistical analysis.

the 1 to 5 p. m. period ($P>0.5$), although there was a mean rise of 0.6 mg. on the race day, with seven of the nine subjects participating in the increase. During the 5 to 9 p. m. race period, however, corticoid excretion uniformly increased over the same period on the control day ($P<0.001$), and all subjects participated in this increase. The increase persisted in the overnight 9 p. m. to 9 a. m. post-race period (Fig. 3).

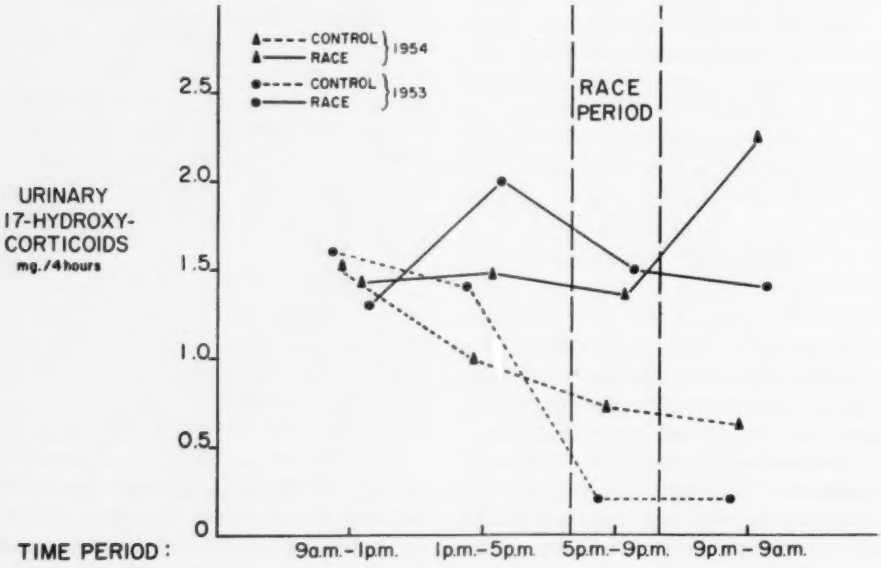

Fig. 3.—The mean urinary 17-hydroxycorticoid excretion in the crews of 1953 and 1954.

In 1954 there was again no significant difference between the control and race day in respect to the 9 a. m. to 1 p. m. and the 1 p. m. to 5 p. m. pre-race specimens (Fig. 3). However, two persons, Nos. 8 and 10, exhibited a striking increase in 17-hydroxycorticoid excretion in this latter period and, indeed, eight of the nine subjects displayed some increase, the mean rise for the group being 0.4 mg. During the 5 to 9 p. m. race period, however, corticoid excretion was, as in 1953, uniformly but less significantly ($P<0.01$) increased. Although all nine subjects participated in this increase, only four did so significantly ($P<0.05$) (Fig. 1). The three persons common to both crews (Nos. 3, 5, and 8) had greater 5 to 9 p. m. race-day increases in 1953 than in 1954. It is to be noted, however, that the absolute level of urinary corticoids exhibited by these three persons during the period immediately preceding the race was higher in 1954 than in 1953! It is noteworthy that the coxswain (1954), who showed the smallest increment of all during the race period, as compared with the same period on the control day, was also the subject with the lowest 24-hour control output of all the subjects, i. e., 1.3 and 1.9 mg. per 24 hours (mean for the group being 4.9 and 5.2 mg.). The 1954 manager (No. 10) displayed his greatest increase in output in the four-hour period prior to the race, which corresponded to the time at which his managerial duties were at their peak.

B. 24-Hour Excretion of 17-Hydroxycorticoids.—1. Control Days: It was noted that on the control day the 24-hour output was lower in 1953 (3.3 mg. per 24 hours) than in 1954 (4.9 and 5.2 mg. per 24 hours). The three persons common to both crews (Nos. 3, 5, and 8) all had a lower 24-hour control-day output in 1953: 2.0, 2.4, and 3.8 mg., as compared with 2.6, 8.3, and 6.2 mg., respectively, in 1954. In 1954 the crew members varied significantly in individual values for control 24-hour corticoid excretion. This individual variation was much less significant in 1953.

2. Control Day *vs.* Time Trials and Varsity Race: In 1953 the changes in urinary corticoid excretion on the time-trial days were similar in direction to those on race day but not as marked, although the difference between the two is not statistically significant ($P>0.05$); this was also true in the 1954 study, in which there was even less difference between the time-trial and race-day changes. It is of interest to note that the mean 24-hour excretion of corticoids on the race day was 6.2 mg. for the nine crew men in 1953 and 6.8 mg. for the three subjects with 24-hour collections in 1954, well within the normal range for subjects not under stress. The real importance of the results lies in the fact that the race, or some associated factor, produced a clear-cut alteration in the usual consistently regular diurnal pattern of corticoid excretion.

In summary, the control-day 17-hydroxycorticoid values in both 1953 and 1954 displayed a significant decrease from morning to evening, conforming to the pattern of diurnal variation found in other subjects. Individual crew members varied significantly ($P<0.01$) from one another in their urinary 17-hydroxycorticoid output (four-hour). Considerably higher control values were noted in 1954 than in 1953. The urinary 17-hydroxycorticoid excretion was similar on the time-trial and race days in both years. The excretion on these days was sustained and hence masked the diurnal decrease characteristically observed on control and practice days. There was a significant increase in the total level of 17-hydroxycorticoids on both time-trial and race days, as compared with that of the control days. The response was noticeably more uniform in 1953 than in 1954. There was no significant difference in over-all 24-hour urinary 17-hydroxycorticoid output between the control and practice days, although a demonstrable increase occurred in a majority of persons.

Changes in Urinary 17-Ketosteroid Excretion

Observations on the changes in the urinary 17-ketosteroid excretion were limited to

TABLE 5.—*Urinary 17-Ketosteroid Excretion*

	Control, No Rowing											Practice Rowing					
	6/6/54					6/13/54					6/12/54					
Subject	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day†	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 P. M. to 9 A. M.*
1	4.4	3.0	3.4	3.3	20.6	3.2	3.0	2.6	3.0	17.7	3.8	3.3	4.5	3.3	21.5	2.9
2	...	...	...	...	...	4.1	3.7	2.8	2.6	18.5	3.5	3.4	3.7	2.9	19.4	3.6
3	3.1	2.9	2.2	2.7	16.2	3.4	3.4	3.0	3.1	19.2	2.9	4.7	3.3	2.4	18.1	3.0
4	1.3	4.7	4.4	4.4	23.7	5.9	3.4	4.0	4.3	26.3	5.7	3.9	3.8	3.6	24.1	4.1
5	3.2	3.8	3.5	3.3	20.3	4.0	3.0	3.6	5.9	28.3	3.3	2.3	3.7	2.0	15.3	2.6
6	3.2	2.7	2.7	2.7	16.8	3.9	2.6	3.4	2.9	18.7	2.9	2.7	2.6	2.6	16.1	2.9
7	...	...	...	...	...	2.9	1.7	1.9	2.6	14.2	2.7	2.2	1.7	3.0	15.5	2.6
8	3.0	3.8	1.8	2.4	15.9	3.5	2.4	2.8	3.4	18.8	2.5	3.3	2.8	2.3	15.5	2.7
9 (Cox)	2.6	2.9	2.6	2.7	16.2	3.6	2.8	2.0	2.8	16.9	3.3	2.4	2.4	2.6	16.0	2.7
Range	1.3-4.4	2.7-4.7	1.8-4.4	2.4-4.4	15.9-23.7	2.9-5.9	1.7-3.7	1.9-4.0	2.6-5.9	14.2-28.3	2.5-5.7	2.2-4.7	1.7-4.5	2.0-3.6	15.3-24.1	2.6-4.1
Mean	3.0	3.4	2.9	3.1	18.5	3.8	2.9	2.9	3.4	19.8	3.4	3.1	3.2	2.7	17.9	3.0
S. E.	0.35	0.27	0.33	0.26	1.1	0.29	0.20	0.23	0.36	1.5	0.32	0.28	0.29	0.17	1.1	0.17
10 (Mgr.)	4.2	2.9	3.2	...	...	...	...	...	...	...	...	...	...	...	...	4.5

* All values, except those for total day, represent milligrams of 17-ketosteroid per four hours, corrected according to creatinine excretion; the over night values are rounded to the nearest decimal point.
† Total day figures are sums of all actual values.

studies on the 1954 crew. The values are expressed as milligrams per four-hour period and are presented in Table 5 and summarized in Figures 4 and 7.

As was seen with the 17-hydroxycorticoid excretion, the 17-ketosteroids showed no significant difference ($P>0.05$) between the control and the practice days and between race and time-trial days. However, there is a significant difference ($P<0.01$) between the values observed on race day and those on control and practice days. Unlike the 17-hydroxycorticoid changes, in which the principal difference appeared in the 5 to 9 p. m. period (although there is a 0.4 mg. difference in the 1 to 5 p. m. period, which is not statistically significant), the significant 17-ketosteroid difference ($P<0.05$) is seen only in the 1 to 5 p. m. period (the period just prior to the race). Again, individual subjects varied significantly ($P<0.01$) from one another in their four-hour output. The diurnal decrease in 17-hydroxycorticoid excretion observed under control conditions did not occur in 17-ketosteroid excretion.

In summary, the urinary 17-ketosteroid output was significantly increased, during the 1 to 5 p. m. period only, on both the time-trial and race days as compared with the control and practice days. There was no significant difference between the values obtained on the practice and control days nor between values obtained on the time-trial and race days.

CHANGES IN UROPEPSIN EXCRETION

Observations on urinary uropepsin excretion, expressed as units excreted in four-hour periods, are summarized in Table 6 and Figures 5 and 7.

A. *Diurnal Variation.*—The level of uropepsin secretion was higher during the night than during the day in five of nine subjects during the control period. This is contrary to the anticipated findings in normal subjects. This reversal of the normal diurnal pattern was evident during the time-trial period in all but one of these subjects. In the three subjects in whom it was possible to obtain complete 24-hour specimens during the period of the varsity race, the night values exceeded those of the day in each instance.

During the race (5 to 9 p. m.) there was no significant change in the values for uropepsin excretion as compared with a similar period during the practice sessions or time trials. Similarly, the mean 12-hour uropepsin output was not significantly different between the control, practice, time-trial, and race days. Of the three subjects from whom 24-hour collections were obtained on the

6/15/54				Time Trial (6/11/54)					Race Day (6/19/54)						
9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M	Total Day	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 P. M. to 9 A. M.*	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day (6/18-19)	Total Day (6/19-20)
3.0	2.4	1.0	15.0	4.4	3.3	3.3	3.5	21.5	3.3	4.2	4.3	2.1	...	18.3	...
2.3	2.4	1.5	16.9	3.4	3.7	3.8	2.9	19.7	5.3	4.0	3.7	3.1	...	26.6	...
3.2	2.8	2.3	17.2	3.2	2.1	3.1	3.4	18.6	3.4	4.0	5.7	3.9	2.5	23.8	21.1
5.9	3.5	4.0	25.8	5.3	8.5	3.9	4.5	31.3	5.0	6.2	5 9	5.7	...	32.9	...
2.9	2.6	2.5	15.9	3.7	4.3	3.6	3.6	22.6	3.1	3.5	3.2	3.6	6.7	19.5	30.4
3.2	2.1	1.6	15.7	3.2	3.1	3.5	2.6	17.7	2.3	3.6	2.6	2.7	...	15.8	...
2.4	1.8	2.5	14.5	2.0	3.0	2.9	2.1	14.3	3.0	3.5	2.7	2.9	...	18.1	...
3.0	1.7	1.9	14.6	3.4	4.0	2.8	2.7	18.3	2.8	2.6	6.6	2.3	2.6	19.8	19.3
2.6	2.0	2.2	15.0	3.9	3.3	1.5	2.3	15.7	...	3.1	3.6	2.3	...	...	...
2.3-5.9	1.7-3.5	1.0-4.0	14.5-25.8	2.0-5.3	2.1-8.5	1.5-3.9	2.1-4.5	14.3-31.3	2.3-5.3	2.6-6.2	2.6-6.6	2.1-5.7	2.5-6.7	15.8-32.9	19.3-30.4
3.2	2.4	2.2	16.7	3.6	3.9	3.2	3.1	20.0	3.5	3.9	4.3	3.2	3.9	21.8	23.6
0.36	0.19	0.28	1.2	0.30	0.61	0.24	0.25	1.7	0.37	0.34	0.49	0.37	...	2.0	...
5.0	3.4	2.9	24.7	4.0	3.9	2.9	3.4	21.0	3.9	4.2	4.5	3.3	...	23.6	...

race day, one (No. 3) displayed a definite increase in uropepsin excretion and a second (No. 8) showed a slight increase. Neither of these increases, however, meets the requirements of statistical significance.

B. *Twenty-Four-Hour Excretion.* — The 24-hour uropepsin excretion in the control period varied markedly from person to person, ranging from 1100 to 13,500 units.

Elevated uropepsin excretion was observed in seven of nine subjects throughout the observation period. The control mean value for the crew was 6800 units. This compares with a mean value of 2300 units for 120 hospitalized patients without gastric disease and with a value of 4700 units for a group of 40 normal college students. Subjects 3 and 4 demonstrated the highest con-

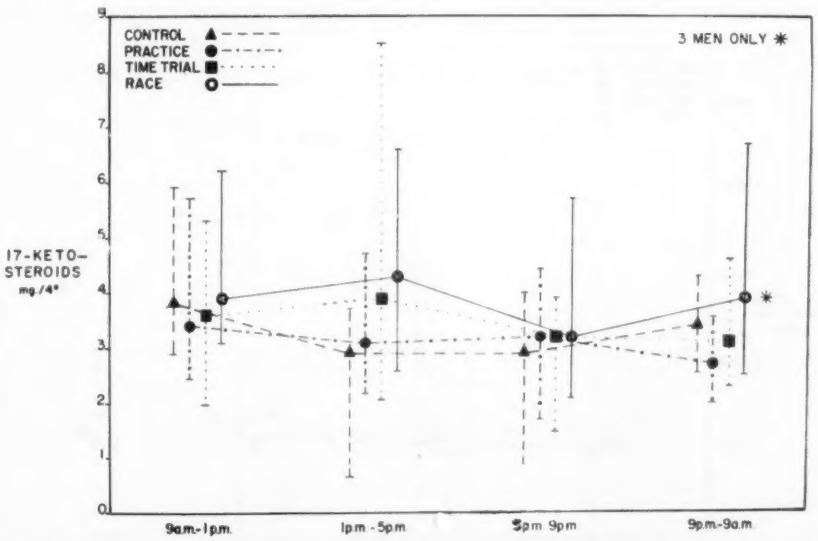

Fig. 4.—This figure represents the mean and range of the 17-ketosteroid excretion of the eight oarsmen of the 1954 crew during the four periods studied. Since only three men collected 9 p. m.-9 a. m. specimens following the race, these values are not considered in the statistical analysis.

trol uropepsin values, i. e., 13,500 and 12,400, respectively. These values simulate the hypersecretion seen in some persons under marked stress or with duodenal ulcer.

The relatively high uropepsin level observed in five of nine members of the crew during control studies immediately preceding the varsity race suggests that the anticipatory stress of the impending race may have been evident even at that time. This thesis is further supported by the observed reversal of diurnal variation noted in five of the nine crew men during the control period.

The subsequent lack of uropepsin response to the stress of the race itself may be explained in part by the initially high control levels of uropepsin excretion. The reversal of the normal diurnal pattern or uropepsin excretion observed in those subjects in whom a 24-hour collection was completed during the varsity-race day is of considerable interest. It is possible that the reversal of the day-to-night excretion pattern may be a more sensitive indicator of uropepsin response to stress than the absolute increase in 24-hour uropepsin excretion.

In previously reported studies [5] in which corticotropin was administered to subjects without adrenal disease, an increase of approximately 300% in uropepsin excretion was associated with an increase of similar magnitude in the urinary ketosteroids. In the absence of a striking rise in 17-hydroxycorticoid and 17-ketosteroid excretion, it is not surprising that we failed to observe an immediate or rapid increase in uropepsin excretion. Regarding the initially high level of uropepsin encountered prior to the race and associated with relatively normal urinary adrenal steroid values, it might be postulated that in this instance a relatively normal level of adrenal cortical secretion exerted a permissive action on the stomach, thus enabling other mechanisms (autonomic nervous system stimuli) to facilitate an end-organ uropepsin response. It is of some interest to note that physical exertion itself does not impair the stomach's ability to increase pepsin output. Increased uropepsin excretion has been demonstrated in a healthy male subject following a 20-minute period of severe exercise.

Correlations Between 17-Hydroxyocorticoids, 17-Ketosteroids, and Uropepsin Values

It appears that certain persons (No. 4) who exhibit a relatively high control 24-hour

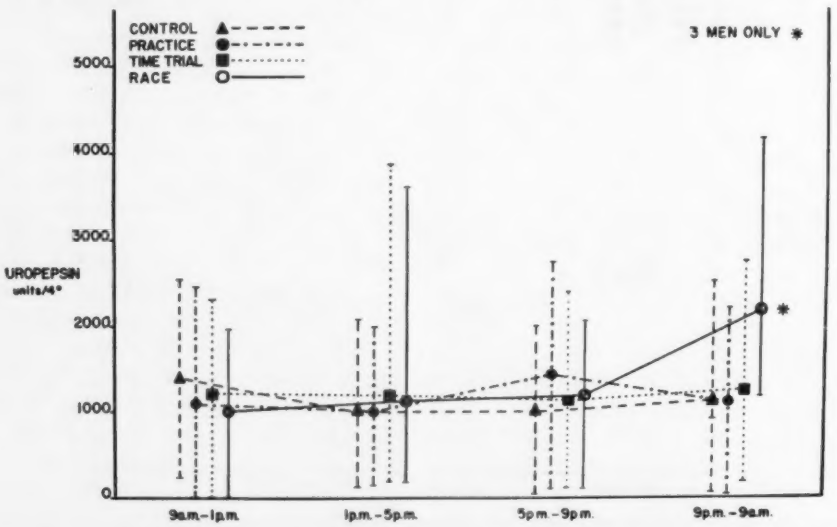

Fig. 5.—This figure represents the mean and range of the uropepsin excretion of the eight oarsmen of the 1954 crew during the four periods studied. Since only three men collected 9 p. m.-9 a. m. specimens following the race, these values are not considered in the statistical analysis.

TABLE 6.—*Uropepsin Excretion in College Oarsmen (1954 Crew)*

Subject	Control, No Rowing (6/13/54)					Practice Rowing (6/12/54)					Time Trial (6/11/54)					Race Day (6/19/55)						
	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day	9 P. M. to 9 A. M.*	9 A. M. to 1 P. M.	1 P. M. to 5 P. M.	5 P. M. to 9 P. M.	9 P. M. to 9 A. M.*	Total Day (6/18-19)	Total Day (6/19-20)
1	1,663	1,299	1,139	1,285	7,956	1,542	1,308	1,839	1,553	9,348	2,244	1,477	1,198	1,594	9,701	1,109	1,101	879	1,818	.....	7,125	.....
2	971	763	888	761	4,905	764	690	1,428	891	5,555	832	906	1,042	771	5,093	1,350	852	.....	.....	.....	.....	.....
3	2,238	2,055	1,888	2,066	12,379	1,668	1,971	2,362	2,285	12,856	2,310	1,306	2,370	2,755	14,251	.....	1,959	3,335	1,733	4,147	.....	19,468
4	2,524	1,394	2,111	2,503	13,538	2,439	2,535†	2,600	2,123	13,943	2,305	3,852	1,889	2,535†	15,651	1,854	1,955	1,532	2,043	.....	11,092	.....
5	1,832	894	856	1,347	7,623	1,282	885	1,690	645	5,792	1,018	776	1,128	1,346	6,960	922	1,231	940	1,286	1,203	6,223	7,066
6	681	1,252	455	947	5,229	480	410	717	467	3,008	653	479	419	520	3,111	546	595	452	583	.....	3,268	.....
7	1,357	851	941	803	5,558	782	667	969	1,186	5,966	819	1,020	1,473	903	6,021	995	968	862	1,244	.....	6,059	.....
8	920	338	643	461	3,284	680	383	1,084	665	4,142	771	681	802	782	4,600	444	500	510	754	1,229	3,096	5,451
9 (Cox)	260	117	25	243	1,131	0	147	89	116	584	0	189	105†	192	870	.....	0	184	.....	.....	.....	.....
Range	260-2,524	117-2,055	25-2,111	243-2,503	1,131-13,538	0-2,439	147-2,535	89-2,600	116-2,285	584-13,943	0-2,310	189-3,852	105-2,370	192-2,755	870-15,651	444-1,854	0-1,959	184-3,335	583-2,043	1,203-4,147	3,096-11,092	5,451-19,468
Mean	1,383	996	994	1,157	6,845	1,071	1,000	1,419	1,108	6,799	1,217	1,187	1,158	1,266	7,362	1,031	1,018	1,087	1,352	2,193	6,144	10,662
S. E.	249	195	219	245	1,347	245	114	267	249	1,480	283	358	240	408	1,652	.....	215	351	207	.....	1,109	.....
10 (Mgr.)	1,568	966	952	.....	.....	1,466	1,014	752	.....	.....	1,122	1,498	1,496	1,450	8,466	1,373	1,375	1,520	1,635	.....	8,649	.....

* All values, except those for total day, represent units of uropepsin per four hours, corrected according to creatinine excretion.
† Calculated according to the method of fitting constants.

urinary 17-ketosteroid excretion (26.3 mg. per 24 hours) also have relatively high control uropepsin values (13,500 units) and that others (e. g., No. 6) with relatively high control urinary 17-hydroxycorticoids (8.5 mg. per 24 hours) have relatively low 17-ketosteroids (18 mg. per 24 hours). Consequently, a multiple correlation analysis was done on both the total and the individual data. This analysis disclosed a highly significant ($P<0.01$) correlation between the levels of 17-ketosteroids and uropepsin for the total data but considerable variation in individual analysis, with only two subjects showing a significant ($P<0.01$ and 0.05) correlation. There is also a significant ($P<0.05$) correlation on the total data between the 17-hydroxycorticoids and 17-ketosteroids, but, again, by individual analysis only four of the subjects show a significant ($P<0.01$, 0.01, 0.01, and 0.05) correlation. Surprisingly, there is no significant correlation ($P>0.05$) between the mean values for total 17-hydroxycorticoid and uropepsin values.

Because in certain persons the correlation with the group showed such marked deviation, an analysis of deviance from the group as a whole bears comment in relation to certain subjects. When compared with the total data, two subjects (Nos. 4 and 2) had strikingly high correlations between 17-ketosteroid and uropepsin values, while two others (Nos. 8 and 6) had strikingly low correlations and one (No. 3) had a strikingly high correlation between 17-hydroxycorticoids and uropepsin. Two other subjects (Nos. 6 and 3) had correlations between 17-hydroxycorticoids and 17-ketosteroids noticeably below those of the group. A lack of correlation between urinary 17-ketosteroids and corticoids has been repeatedly observed in the past.‖

Although these findings are of great interest, they cannot be definitively interpreted because the correlation coefficients varied significantly ($P<0.001$) from person to person; thus interpretive correlations based on individual and total data comparisons would have questionable statistical significance.

‖ References 19 and 20.

Complementary Studies

To facilitate interpretation of the data obtained in the crew study, additional experiments were carried out. These may be grouped as follows: (1) observations which would permit comparison of the crew race with other forms of exercise and (2) studies designed to explore the possibility of altered metabolism (? increased "utilization"¶) of adrenal steroids as part of the response to exercise.

Long-Distance Running.—The changes in circulating eosinophiles and 17-hydroxycorticoid excretion were studied in one 28-year-old normal untrained man who participated in a three-hour, 17-mile run in which no competitive stimulation was present. Whereas the eosinophiles did decrease appreciably (74%), there was no significant increase in urinary 17-hydroxycorticoid level. However, the normal anticipated diurnal decrease in hormone excretion did not occur during this period, thus suggesting some degree of adrenal activation over the baseline control value.

The 17-hydroxycorticoid response was also measured on a normal trained male subject during the running of the highly competitive 26-mile Boston Marathon race in 1954. Again, although no increase in 17-hydroxycorticoid excretion was observed, the anticipated diurnal decrease was obliterated.

Studies on 17-Hydroxycorticoid Excretion in Sweat.—Because of the marked weight loss observed in these subjects in association with prolonged, severe exercise, it was felt advisable to ascertain whether or not sweat contains measurable quantities of corticoid material. A study carried out on a 25-year-old healthy man indicated that

¶ The term "utilization" as we employ it in this paper is a generic one indicating possible altered metabolism of adrenal steroids in such a way as to render the excretory product nonmeasurable by the methods employed.

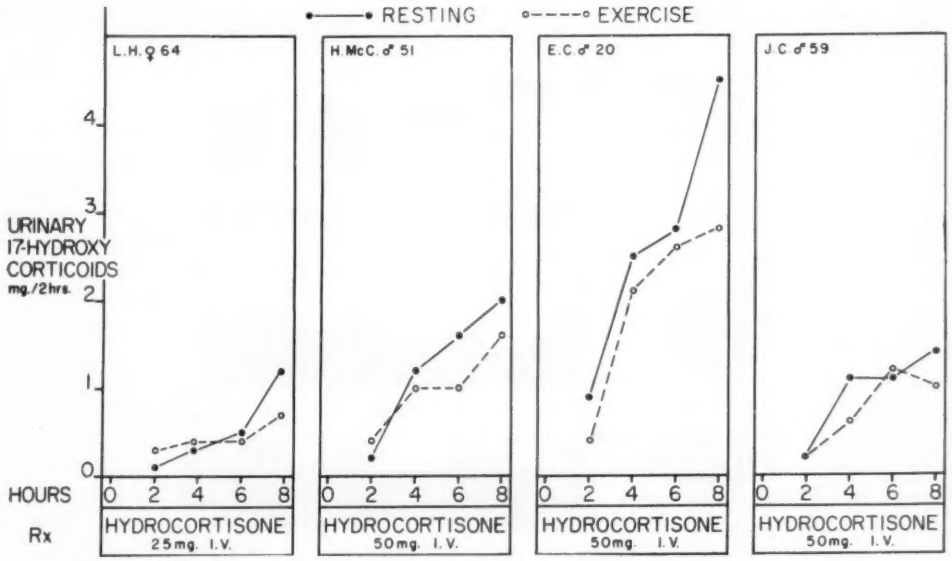

Fig. 6.—The recovery of 17-hydroxycorticoids in the urine of patients with Addison's disease during hydrocortisone infusion at rest and with exercise.

no 17-hydroxycorticoid material could be detected (by the method employed for assaying urinary steroids) in his sweat collected during severe exercise. It appeared from this study that loss of 17-hydroxycorticoid in sweat probably did not account for the failure to observe a greater increase in urinary steroid excretion.

"Utilization" Studies.—In an attempt to clarify the effect of exercise per se on the urinary excretion of 17-hydroxycorticoids, the 17-hydroxycorticoid excretion of a 64-year-old female patient with proved Addison's disease, receiving 25 mg. of hydrocortisone intravenously over an eight-hour period, was compared at rest and during bicycle-pumping exercise (Fig. 6); a small decrease in the quantity of 17-hydroxycorticoid excreted during exercise was observed. This was further suggested in three other patients with Addison's disease who received 50 mg. of hydrocortisone intravenously over a period of eight hours, with and without exercise; in each instance a small (1.5-2 mg.) decrease in 17-hydroxycorticoid excretion was noted during the period of exercise (Fig. 6).

The 17-hydroxycorticoid excretion was studied in another patient with Addison's disease, a 51-year-old man who received 50 mg. of hydrocortisone intravenously over a six-hour period, both during a control period and during the stress of twelve dental extractions under general anesthesia; similar excretory patterns were noted under both circumstances, suggesting that the stress of this particular procedure did not alter the steroid excretory pattern.

The 17-hydroxycorticoid excretion of an 18-year-old female patient with unilateral adrenal hyperplasia proved at operation was measured both before and after exercise consisting of climbing and descending stairs and during "psychological frustration" of attempting to master a 10 key-10 letter association problem. In the half hour of trials she was given incorrect hints on learning the task, continually interrupted (through earphones and audograph record) to hear how many keys were usually mastered by this time, and generally distracted. She was obviously distressed, perspired a great deal, failed to master a single key-letter association, made 383 errors in 20 minutes, and

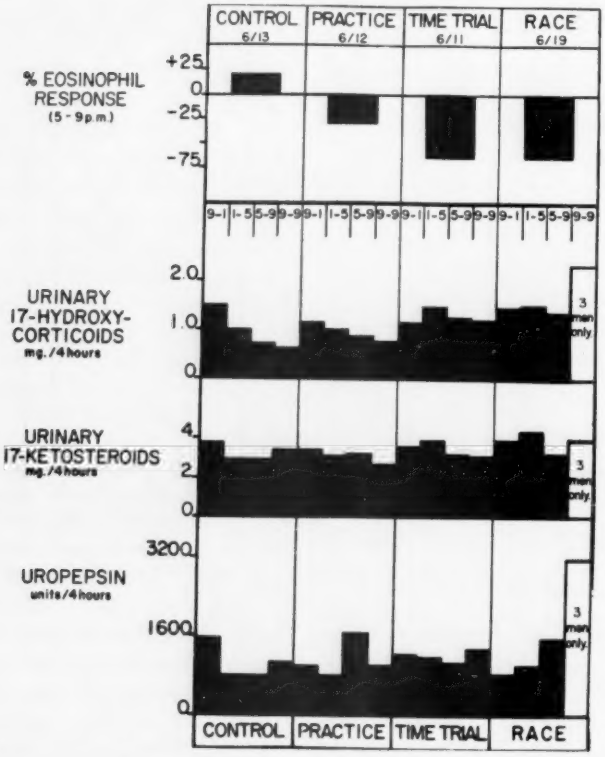

Fig. 7.—The mean metabolic response of the eight oarsmen and cox of the crew of 1954.

was depressed for a full day following the frustration and insult to her ability to learn. No change could be detected in diurnal pattern of 17-hydroxycorticoid excretion.

In order to study the "utilization" of steroids further, exposure to cold was employed as a stress mechanism. The eosinophile and 17-hydroxycorticoid response were measured on one subject exposed to 4 C without added clothing for a four-hour period; these results were compared with those obtained upon testing the same subject with corticotropin prior to and during similar exposure to cold. There was no increase in urinary 17-hydroxycorticoid excretion as a result of exposure to cold, and the urinary 17-hydroxycorticoid response to corticotropin stimulation was quite similar before and during the same cold exposure.

METABOLIC INTERPRETATIONS

Evidence of an Adrenocortical Secretory Response to the Race or to Some Factor Associated with It

Prima facie evidence of increased adrenocortical secretory activity in response to the varsity race consists of the increase in total 17-hydroxycorticoid excretion in the urine during the race period as compared with the values obtained during a similar period under control circumstances. Of added interest is the fact that the increased excretion of 17-hydroxycorticoids observed during the late afternoon and early evening on the day of the race completely masked the diurnal decrease characteristically observed in these persons and in other normal subjects at this time (Fig. 7). The inability to follow blood steroid levels in these athletes during their period of exercise and the unknown factors concerned with intermediary metabolism of

adrenal cortical hormones under conditions of stress necessitate some degree of conservatism in this interpretation. Supplementary experiments carried out in other forms of exercise by the authors, as well as the studies of others,# support the probability, however, that the urinary changes under these circumstances do reflect increased adrenal cortical activation. Additional indirect evidence consists of a rise in 17-ketosteroids observed in the period immediately preceding the race and the consistent and remarkable fall in the level of circulating eosinophiles. Of particular interest is the fact that on race day, with only anticipation of the race as a stimulus, there was a decrease in the eosinophile count between 9 a. m. and 5 p. m. (Table 2) along with an increase in the excretion of total 17-hydroxycorticoid and 17-ketosteroid material in the urine (Fig. 7).

Status of "Increased Utilization" During Stress as a Factor Modifying Steroid Excretion

Studies on patients with Addison's disease undergoing major operative procedures have failed to reveal a significant alteration in the excretion of total 17-hydroxycorticoids. In these studies the patients were maintained on a constant level of cortisone, which was kept up during a control period and throughout the operative procedure. There appeared to be no significant difference in the quantity of 17-hydroxycorticoid material excreted by a normal subject given corticotropin under control conditions and at a later date while being exposed to cold (4 C for four hours). Recent experiments [23] with isotopically labeled steroid appear to indicate that the renal handling of steroid material under stress is not appreciably altered by the forms of stress investigated. Studies carried out on a normal subject indicate that no appreciable amount of hormone is lost in sweat.[6] On the other hand, in experiments in which we studied excreted products from a relatively small dose of hydrocortisone infused in patients with Addison's disease over a prolonged period with and without exercise, somewhat lower values for urinary total 17-hydroxycorticoid during the period of exercise were revealed. In these experiments very small quantities of hormone were used in an attempt to enhance this difference. It would appear that an actual increase in urinary 17-hydroxycorticoid in all probability reflects increased adrenal cortical secretory activity, whereas no change in the urinary values might also be consistent with some degree of increased adrenal secretory activity together with altered metabolic degradation or excretion.

Quantitative Relationship Between the Decrease in the Level of Circulating Eosinophiles and the Increase in 17-Hydroxycorticoid Excretion

Earlier studies in normal subjects given corticotropin indicated that with a 40% to 50% fall in eosinophiles one might anticipate an increment of 0.5 to 1 mg. of urinary 17-hydroxycorticoid material. In studies carried out on the day of the varsity race, the rise in 17-hydroxycorticoids amounted to 0.73 mg. per four hours, whereas the eosinophile fall amounted to 70%. It would appear from this that factors other than the adrenal cortex in all probability contribute to the eosinopenia, the most likely being epinephrine. When reliable methods are available for quantitative adrenal medullary hormone measurement, it will be of great interest to ascertain what proportion of a given eosinopenia is mediated by adrenal cortical steroids and what proportion is mediated by factors other than corticoids, i. e., epinephrine, etc. It is likely that individual subjects will respond differently to an intense stress such as a varsity crew race with respect to the degree to which the adrenal cortex and medulla are activated.

Reference 21 and Elmadjian, F.: Adrenocortical Function of Combat Infantrymen in Korea, in Reference 22, p. 627.

Are the Adrenal Cortical Activation and the Eosinopenia Stimulated Primarily by Physical Exercise or by the Psychological Stress Associated with the Race?

That physical activity alone is not the major factor responsible for adrenal activation and the marked fall in circulating eosinophiles is suggested by the minimal response observed on several occasions when the race course was covered in a practice session. During these exercise periods, the time and the muscular effort expended closely approximated that which was exhibited during the varsity race. Favoring the importance of psychological factors is the observation that the coxswain and the manager displayed an eosinopenia as marked as that of the crew members.

Psychological Observations

Group Rorschach

Extensive use of the Rorschach test for many years has demonstrated that the way a person perceives the color and form on the test cards reflects his emotional response to life situations. The number of answers and the percentage relationship in the various categories establish a profile for each person. This profile provides important information concerning the balance of emotional repression versus expression and of emotional control versus emotional discharge. In general, the perception of form is related to control, color is linked with the discharge of emotion, and the perception of moving forms connotes the ability to use ideas constructively.

The composite (or averaged) personality profile for the 1954 crew (Fig. 8) compares closely to the statistical profile obtained by administering the Rorschach test to thousands of "normal" persons and averaging the results. In spite of this congruence of averages, however, the ranges from member to member of the crew varied greatly and included patterns outside of what is usually considered to be the normal range. For example, the total number of responses ranged from 8 to 54, with a mean of 29. These two extremes represent a great difference in capacity for psychological response: from that of a blocked very anxious person to that of a highly responsive, active person.

In much the same way, the capacity for emotional expression, as indicated by the number of "color" responses, varied widely, even though the composite average of the crew approximated the "normal" personality.

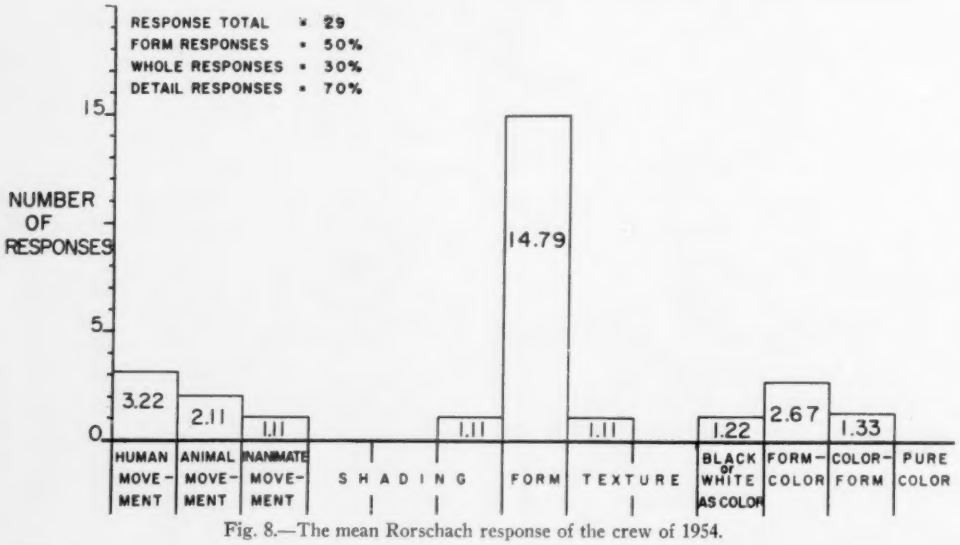

Fig. 8.—The mean Rorschach response of the crew of 1954.

Here again the range extended from no color responses to eight; in terms of capacity for emotional response, these differences are significant.

Thus, while presenting a composite group that perfectly fits the "expected" pattern, the Rorschach findings indicate that this group embraces persons with widely divergent personality characteristics and manner of response to life situations. These findings in 1954 are similar to the results obtained in the study of the 1953 crew, and, averaging the results, the 1953 composite Rorschach profile is comparable to the 1954 composite; the only difference is a narrower range of variation in 1953.

A comparison of the two Rorschach tests, before and during the intensive training for the final race in 1954, revealed several significant shifts. Seven members of the crew were included in the group Rorschach test given six weeks before the race and again one week before the race. Of the seven, five showed an increase in percentage of responses determined by form alone in the second test. A decrease in the color-form ratio indicated that five (not the same as above) had become less spontaneous and less able to express themselves freely. Six of the seven showed an increase in "detail" responses at the sacrifice of integrated "whole" responses. Thus the training regimen appeared to have intensified the utilization of repressive mechanisms, as indicated by an increase in the number of form responses, and to have resulted in an inhibition of emotional expression, as shown by a decrease in the color-form ratio. The increased perception of details further suggests that anxiety was increased and that the men were responding to a more strictly defined and narrowed field. These changes are compatible with the experience of crew members during the period of intensive rigid training which included strict limitation of behavior.

Three of the above subjects had been members of both crews. The Rorschach tests just before the race in 1953 and in 1954 in one of these men showed a tendency toward greater control and use of repression in contrast to the Rorschach test six weeks before the race (in 1954). In the other two crew members, this could not be demonstrated with as much certainty. The general trend could be defined more accurately in comparing the whole group six weeks prior to the race and just before it.

Thematic Apperception Tests

The TAT findings do not lend themselves to numerical comparison of individual differences. It can be said, however, that capacity for imaginative response varied widely among the members of the crew. Some were able to elaborate dramatic stories with ease, while others found this much more difficult. The stories suggested quite differing individual motivations for choosing a group sport like crew.

The picture of a rope climber, for instance, elicited a variety of motivations for athletic activity. One man perceived sports as a test of general success in life, a method of determining one's fitness and capabilities. Another indicated that athletics was a necessary preparation for competition in a hostile world. A third man expressed the feeling that the world was an arena where only the fit survive. Preparation consisted of toughening and proving one's invulnerability through athletics. Not all the suggested motivations, however, were of this type. Exhibitionism and the plaudits of others were also indicated as drives for athletic participation. Two men, on the other hand, gave stories ridiculing and devaluating participation in athletics.

The picture with possibilities for group action failed to elicit expressions of enthusiasm. A somewhat more positive or constructive response to this stimulus for thoughts about a group of men had been expected. Only one member expressed a positive group attitude, while three others were lukewarm in their expressions. It may have been significant that this corresponded to doubt mentioned by several of the men during their personal interviews with the psychiatrist about the ability of this particular crew to "row together."

Personal Interviews

During the personal interview with the psychiatrist, all of the men were friendly and each of them seemed to be doing his best to cooperate. The majority of the men appeared at ease, although two found it difficult to talk spontaneously unless they were asked occasional questions. One of the men responded to the interview as though it were a challenge to demonstrate his capacity for psychological insight. This was apparently characteristic of his performance in other situations. Another man seemed uneasy until he had decided to mention certain aspects of his personal background which had been particularly disturbing to him.

Background.—Each man was asked about his school preparation before coming to this university. All of the men had graduated from well-known eastern private schools. Five of the men were sons of alumni of this university, and the fathers of four crew members had themselves rowed on crews when they were at college. This information was usually given when each man was asked how he had happened to come to this particular university and go out for crew.

Personal Implications of Becoming an Oarsman.—Each man in the group expressed some feeling about having to give up other interests and activities in order to row on the crew. One man explained, "It's a terrific strain mentally and physically. You've got to be willing to give everything up for it. Rowing has to come first and your studies second." Another man remarked, "In terms of grades, there's a decided price you pay. You have to decide eventually which one of the various commitments of your time is the most personally relevant to you, and in terms of rowing I think the decision generally has to be made in terms of—in favor of rowing. You don't go out for it to improve your physique, you don't go out for it for any sense of glory, you just do it from a compulsive drive." A third man stated, "When I first came to college, I was going to be a doctor. If I really wanted to be a doctor, I'd have to give up crew. Practically speaking, the only way I could get out of rowing was by leaving college, the obligation is so great. Generally the boys who've been taking chemistry 20 [premedical course] have done rather badly in crew that year. They've had to sacrifice something." A fourth man commented, "I went out for honors and tried to write a good thesis. I found that it was impossible to do this and row too." A fifth man said, "It really hurts sometimes when you have to spend so much time in the afternoon, three hours every day. Sometimes I really feel that I'd give anything to be able to spend that time reading." At least two of the men were very much aware of the deprivation imposed by having to diet in order to keep their weight down.

A number of the men gave vivid descriptions of the demands on an oarsman during a race. One man remarked, "The endurance, I think, comes from the amount of sleep that you backlog. I think it's the most grueling sport in the world." Another man said, "I'd like to think that I've gotten a letter in the toughest sport that there is. I think it's the most grueling of any sport." According to a third man, "It's a very tough sport and occasionally very painful—the skin gets off your hands. You have to row for a couple of miles on raw skin. If the boat's off balance, your fingernails catch in the upper part of your leg and sometimes you go deep enough to get blood running down your leg when you're rowing."

The comments of one of the men illustrate the tendency for individual thoughts and feelings to disappear during the race. "You've got to get out of your mind the fact that you might fold. The only way to row is just to forget, first of all, how you feel because that's terrible and you immediately come to the conclusion you feel awful. You also have to forget what you're doing. All you can do is look at the fellow in front of you."

A number of men described strong feeling of guilt at times when they felt that they had not done their best. "It's a bit of a tension whether you can really produce your best

all the time—that's the major tension." Another man remarked, "Individuals usually take it to heart when something goes wrong. They usually take it quite personally and your major mental fight is to try and realize that it usually is not necessarily any one person's fault unless they fell out of the boat or caught a very bad 'crab' which was completely unavoidable."

Psychological Aspects of Rowing Together.—Robert F. Herrick,[24] famous former coach of the Harvard crew, makes a note on rowing in the dark which vividly conveys the basic rhythmic unity achieved by a well-trained crew. He reports, "From time to time I have known crews to test this out by rowing with their eyes shut. When a crew that has practiced a long time together does this, they seem to find no difficulty in keeping perfect time with the stroke for several strokes without watching the motion of any other man."

Many of the men who were interviewed in 1954 commented on the importance of the integrated performance of the crew as a group. They contrasted their own crew unfavorably in this regard to the crew of the previous year. "Last year we had a boat that was 'swinging' very well and it was so efficient that the last two miles you didn't have to pull quite so hard and yet the swing would carry the boat, which is the whole secret. This year we have a boat which does not swing. We have a lot of power but everybody . . . I mean, it's a lot of apes. If you can get an ape to swing, why it's wonderful, but if he doesn't you're lost and at the moment we're lost." Another man explained, "It doesn't necessarily follow if you take your best eight oarsmen and put them in a boat that it will be the fastest boat. It depends to a certain extent on what those eight oars are like mentally." A third man commented, "This isn't really a contest of strength because you start with the supposition that these guys are all strong. The question is how they apply their strength in a coordinated effort." The effect of this integration on the individual was described by another man, "When things start to go wrong, you tend to retreat into yourself, sort of like a turtle—you put your head between your shoulders and you row like mad and you revert to pure physical violence. You revert to pressure on the oar, which may not be what's needed at all."

PSYCHOLOGICAL INTERPRETATION

Psychological stress results from any external threat, from any intensification of instinctual drives, or from any heightening of the demands of conscience which challenges the capacity of the person to maintain a balance between his needs and his satisfactions. Thus a situation like the race becomes stressful for a person in terms of what it means to him. This, of course, depends upon his personality and the way he has been trained.

In contrast to combat conditions, the members of the crew were not, of course, subjected to any threat of mutilation or loss of life. Psychological stress could only result from the intense focusing of energies in accordance with what each person demanded of himself in order to meet the requirements of the group effort.

The varsity crew constitutes a highly organized group with a long and famous tradition. Each member of this group is expected to channel his activities according to a clearly defined pattern. As one of the men put it, "You go through the same standard motion which is set the first time you ever row in a boat. You're rowing and you're rowing backwards all the time and never see where you're going." The function of leadership is divided among the coach, the cox, the stroke, and the captain. During the final weeks of training, the coach and the members of the crew eat all of their meals together at a special table in a private dining room. This helps reenforce the group ties. All the members of the crew, except the cox, row and keep silent during the race. That the cox does neither may help to explain why he is traditionally tossed into the river by the winning crew—appar-

ently a manifestation of the group need for a scapegoat.

It is well known that oarsmen maintain their identification with the crew to a remarkable extent for the rest of their lives. This was well exemplified recently when a varsity crew returned to row at Harvard 40 years after graduation. As one of the 1954 crewmen explained, "I think the reason that crew attracts the more mentally sensitive, intellectual people is partially the friendships." Another man spoke of the "bond you get—you get a terrific kick out of it. It just sort of fascinates me, everybody moving together and working as one. It's almost like another club or something, rowing. You build up terrific friendships between everybody. If the boat goes well, it happens almost immediately." The potential ambivalence of this relationship was expressed by one man, "You sort of have to get along with your crewmen, you're closer to them. In football or in baseball or in hockey—regular contact sports—you have a whole hundred yards to bustle about in, and in crew you don't have very far to go. Personalities become very exaggerated as the sport wears on—as the season wears on. It can be quite fortunate and can be difficult. It has its attractive aspects and it has its unattractive aspects, too, with personality clashes."

Several of the men gave enough information about their backgrounds to indicate that they had been motivated to go out for rowing by an urge to resolve certain personal problems. A wish to resolve feelings of personal rivalry seemed to explain at least one of the men's enthusiasm for crew because, as he remarked, it requires "such terrific subordination of your selfishness." As another man expressed it, "You're only a good oarsman in your ability to lose your own personal motives and ideas in the world of the boat as a whole. In football you can be a good football player on a bad team—you can sort of stand out. If you stand out in a crew, you're generally doing something wrong."

Summary of Psychological Findings on the Crew

The members of the crew included a wide variety of personality patterns.

Varsity rowing represented a major emotional investment for each man.

Training intensified the involvement of each man in the efforts of the group and, especially during a race, individual thoughts, feelings, and differences receded and tended to disappear.

The amount of stress for each person seemed to be influenced by the integrated performance of the crew as a group.

Prior to the race in 1954 some members of the crew felt that they were not "rowing together" and the group had evidently failed to achieve effective integration of individual differences.

Supplementary Studies on the Effect of Psychologic Stress on Adrenal Cortical Activation

In an attempt to measure the adrenal response to psychological stimulation, without an appreciable increase in physical exercise, the urinary 17-hydroxycorticoid and circulating eosinophile responses were measured in 23 normal medical students during the second-year final examination in pathology and in four other medical students presenting a case for the first time before the assembled senior staff. No consistent change in circulating eosinophiles nor in 17-hydroxycorticoid excretion could be detected in these subjects. One of the twenty-three students exhibited a near "panic" reaction to the examination and demonstrated a fall in circulating eosinophiles of 79% and an increase of 1.6 mg. per four hours in 17-hydroxycorticoid excretion. Five Ph.D. candidates were similarly studied during their general examinations. Four responded with a decrease in circulating eosinophiles ranging from 50% to 85%. The fifth exhibited a low level (77/cu. mm.) initially. None of these persons exhibited an increase in urinary 17-hydroxycorticoid excretion over the values obtained on specimens collected at a similar time on a control day.

The eosinophile and 17-hydroxycorticoid response was also measured on a group of 19 physicians, social workers, and secretaries during a control period and during exposure to a 15-minute movie vividly depicting primitive tribal rites. No uniform change in circulating esinophile levels, in 17-hydroxycorticoid excretion, nor in any correlation between these two could be clearly demonstrated.

Concurrent observations of behavior changes and of adrenocortical variations in a cyclothymic patient during a period of two years,[26] as well as other studies to be published, have, on the other hand, demonstrated a correlation between sustained emotional changes and variations in the pattern of the 17-hydroxycorticoid excretion.*

The failure to demonstrate evidence of marked adrenocortical activation among the persons subjected to apparently moderate stress and the successful demonstration of such activation in patients undergoing sustained emotional upheaval or in persons under the stress of unusually severe group pressure (e. g., the crew) suggests a tentative hypothesis. Perhaps the psychological mobilization for an immediate emergency ("fight or flight") is physiologically represented by activity of the adrenal medulla. A psychological response involving a shift in the balance of relatively primitive biological energies and their psychological control, on the other hand, may be reflected by adrenocortical activation. There would be every reason, of course, to expect both medullary and cortical influences to be present in varying degrees. From a psychological point of view, this would correspond to the combined influence of individual character and of the relatively less differentiated biological energies present in everyone. This interpretation of the data and the suggested hypothesis are offered within the limitations of the available biochemical methods.

* Fox, H. M.: Physiological Response of the Adrenal to Psychological Influences as Indicated by Changes in the 17-Hydroxycorticosteroid Excretion Pattern, in Reference 22, p. 612.

METABOLIC AND PSYCHOLOGICAL CORRELATION

In their study of the 1950 varsity crew, Renold and co-workers [4] concluded that in well-trained persons emotional stress, either alone or in combination with muscular activity, may induce pronounced adrenal stimulation. This previous study was based on the measurement of changes in the circulating eosinophiles. Observations of the urinary excretion of 17-hydroxycorticoids of the members of the varsity crew in 1953 and again in 1954 indicated more directly that an activation of the adrenal cortex had very probably taken place. In the earlier study (1950), it was noted that the eosinophile levels of the coxswain and the coach fell as much during the period of the race as did those of the eight members of the crew. The responses observed in the coach and the coxswain suggest that the physical exertion of rowing was not the major stress involved in evoking the striking eosinopenia observed in all members of the crew.

There were a number of findings in the 1954 crew study which emphasized the importance of psychological factors as a cause of adrenal activation. The metabolic response of the crew on practice rowing days did not differ appreciably from that noted on control days on which there was no rowing. In contrast to this, there was evidence of a significant increase in urinary 17-hydroxycorticoid excretion during the time trial as well as the varsity race. As indicated previously, the physical exertion in these two types of competition was quite comparable to that experienced on the "practice days," although the psychological setting was, of course, entirely different.

On the afternoon of race day, prior to the actual race, convincing evidence of adrenal stimulation was observed, i. e., a decrease in eosinophile count in conjunction with an increase in corticoid excretion. The latter was of sufficient magnitude to obliterate the diurnal decrease so characteristically observed during the latter part of the day (Fig. 7). Two subjects had a striking increase in corticoid excretion during the

four-hour period preceding the race. The increase in one of these persons (the crew manager) corresponded to the peak of his managerial duties and did not involve any unusual physical exercise. The increase in the other person (a member of the crew) undoubtedly reflected the anticipation of the race itself. In these two instances, eosinopenia accompanied by increased urinary 17-hydroxycorticoid excretion occurred in the absence of extreme physical stress. For comparative purposes, studies were carried out on normal persons subjected to situations involving primarily psychological stress, e. g., Ph.D. candidates during their general examination and hospital personnel exposed to movies illustrating primitive tribal rites. Under these circumstances, a fall in eosinophile count without significant rise in urinary adrenal corticoids was observed. These changes suggest increased adrenal medullary, rather than adrenal cortical, activity.

One of the most striking metabolic findings was the individual variation in the 1954 crew members on both their pre-race and their race responses. Although the pre-race response of individual members varied in 1953, the metabolic response to the race was surprisingly uniform (Fig. 1). Psychological studies in 1953 had demonstrated a wide variation in personal make-up. In 1954, individual variation was apparently just as great. A number of the men, including two of the members who rowed both in 1953 and in 1954, observed a marked difficulty in "rowing together" in 1954, as contrasted to the previous year. These comments were made during personal interviews prior to the race. The fact that it was necessary to make three substitutions within 10 days of the race in 1954 clearly indicated difficulties which had not been present in 1953, when the membership of the crew had remained the same for many months. It is possible that this uncertainty may have contributed to the strikingly higher control steroid output in 1954 as compared with 1953. This was true for the group as a whole and for the three persons who rowed in both years. During the 1954 race, the group had evidently failed to achieve effective integration of individual differences, in contrast to 1953 when the men felt they were "rowing together," the metabolic response was more noticeably uniform, and the race was won.

Crowds as well as organized groups have been studied by many psychological observers. It is well known that in a group the emotions of an individual person may, under certain circumstances, become extraordinarily intensified, with a marked reduction in his capacity for intellectual criticism and control. This seems well illustrated by the remark of the crew member who stated that during a race he "concentrates" but does not "think." The crew constitutes a highly organized group. Observation suggests that the effect of membership in this group not only intensifies the emotions but that during the race each man subordinates his capacity to think for himself. The present study represents an early attempt to make biochemical observations of group processes.

It seems likely, furthermore, that participation in this kind of group activity may result in the temporary submergence of individual differences of character by relatively primitive biological drives.[25] Individual character structure is, of course, exactly what the Rorschach test differentiates. On the other hand, an alteration in the rhythmic cycle of relatively primitive biological drives could be represented by changes in the diurnal excretion pattern of 17-hydroxycorticoids. An obliteration of the usual diurnal decrease in 17-hydroxycorticoid during the afternoon and evening was actually observed on race day in both years. Training seemed to intensify the involvement of each man in the efforts of the group, and, especially during the race, individual thoughts, feelings, and differences receded and tended to disappear. Statements of the men during their interviews, including those who have been members of both crews, suggested that this had not been achieved nearly so successfully in 1954.

In addition to these correlations between the metabolic and psychological findings on the group as a whole (Figs. 7 and 8) a cor-

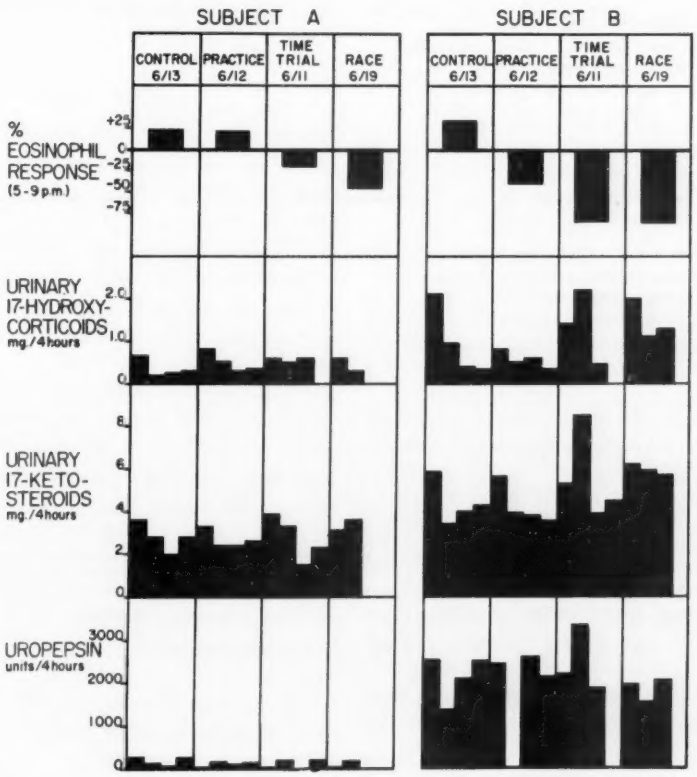

Fig. 9.—The metabolic response of two members of the crew of 1954. The periods of urine collection illustrated are from 9 a. m. to 1 p. m., 1 to 5 p. m., 5 to 9 p. m., and 9 p. m. to 9 a. m. All charted values represent the amount of material excreted per four hours.

respondence between the biochemical findings and the psychological make-up of at least two persons could also be established (Figs. 9 and 10). One of the men showed a wide divergence from the other members of the crew in regard to his responses in the Rorschach test. He produced, for example, only eight responses to the 10 ink blots (Fig. 10*A*), whereas the mean value for the crew was 29 (Fig. 8). Such a small number of responses is usually associated with a general emotional inhibition. This was also manifested in the Thematic Apperception Test, where little freedom or spontaneity of imagination was expressed. These responses indicate blocking and anxiety. There was a similar divergence from the group in his metabolic response (Fig. 9*A*). This was characterized by urinary 17-hydroxycorticoid values at the lowest level of the normal range and a urinary uropepsin value below that seen in normal subjects. Furthermore, the urinary 17-hydroxycorticoid response to the race day was the smallest observed in the group.

Another crew member gave 45 responses to the Rorschach test (Fig. 10*B*). This is considerably above the group mean of 29 and is the second largest number of responses. In spite of this, he gave only one "color" answer. Failure to respond to color, particularly among a large number of responses, is usually associated with a reluctance to express personal feelings outwardly. This seemed reflected in his comment about a figure he perceived in one of the Rorschach cards: "It looked like he was calm on the outside and barking on the inside." During

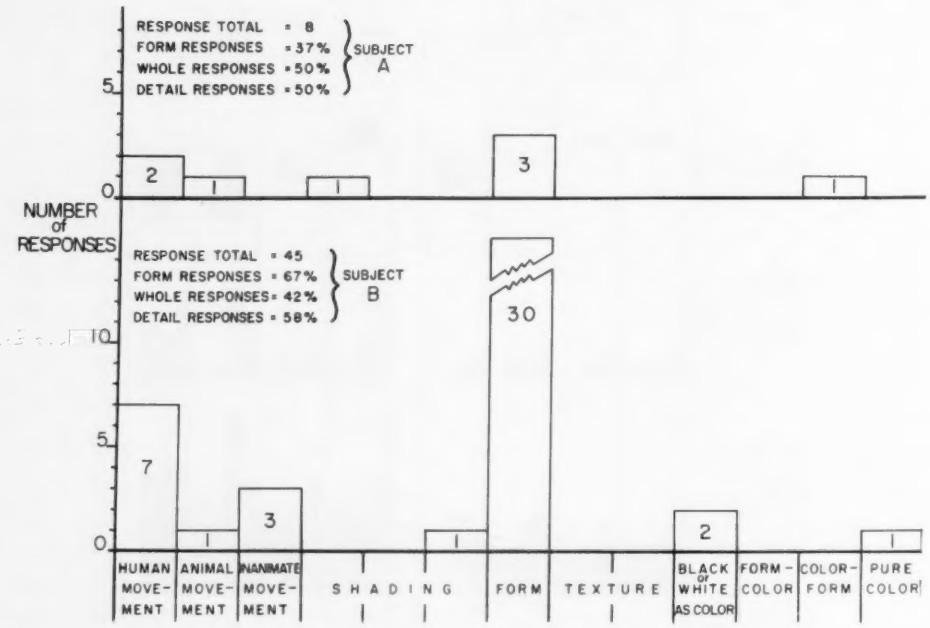

Fig. 10.—The Rorschach response in two members of the crew of 1954.

his personal interview with the psychiatrist, he confessed that during the last part of an earlier race he felt as though he was going "to vomit every other stroke." His metabolic response (Fig. 9*B*) was characterized by the second highest increase in 17-hydroxycorticoid excretion on the time-trial and race days as compared with the control and practice days. In addition, his urinary uropepsin levels were the highest noted in the group, 13,500 units per 24 hours, which is considerably above the normal range. His urinary 17-ketosteroid response was similarly the highest noted in the group. This subject does not express his personal feelings and perhaps sees himself as "calm on the outside while barking on the inside," which may be reflected in his exaggerated metabolic response. His tendency to vomit during and after the race is of particular interest in view of his high uropepsin levels!

The apparent relation between the psychological and metabolic findings in these two persons is of considerable interest. In the remaining members of the crew similar correlations could not be brought out so clearly. More extensive observations will be required in these persons before dependable correlations can be anticipated.

The over-all study provides metabolic and psychological evidence suggesting that a successful crew endeavor depends not only on the physical performance of the rowers but also on how much each crew member has been able to resolve his conflicts concerning the personal implications of rowing and on how far he can merge his individual drives with the activity of the crew as a group. The contribution of college rowing to the educational development of those who go out for it, on the other hand, would seem to depend on how high a price each man has to pay in order to make such a major emotional investment. The answer would presumably vary from one individual to another and would require extensive study beyond the scope of these observations.

CONCLUSIONS

The stress of crew racing, as well as other forms of physical and psychological activity,

has been found to result in an increase in the total 17-hydroxycorticoids in the urine, therefore presumably indicating an increase in adrenal cortical activity.

The increase in total urinary 17-hydroxycorticoids was not great enough to account for the eosinophile fall in some persons, when compared with standard corticotropin responses. This discrepancy could be explained by either increased "utilization" of endogenous steroid during exercise or by elaboration of other eosinopenic factors, such as epinephrine, or by a combination of both factors. Final interpretation of this cannot be arrived at with the present data.

The urinary 17-ketosteroid output of the 1954 crew members was significantly increased only during the four-hour pre-race and pre-time-trial periods.

The urinary uropepsin levels were found to be elevated in a majority of the crew members throughout the observation period.

The importance of psychological factors in causing adrenal cortical activation was brought out by the fact that corticoid output on practice days, on which physical exercise was roughly comparable to the race and time trials, was not increased over the control days, on which there was no rowing. There was, however, evidence of significant adrenal cortical stimulation during the time-trial and race days, when the psychological setting was, of course, entirely different.

Varsity rowing represented a major emotional investment for each man and, therefore, rowing in the race presumably constituted a severe psychological stress for all.

The metabolic response of the individual crew members of the race in 1954 was noticeably less uniform than in 1953. Moreover, the mean urinary 17-hydroxycorticoid levels of the entire crew, and the levels of each of the three persons common to both crews, were higher in 1954 than those in 1953, indicating perhaps greater pre-race tension in 1954.

Prior to the race in 1954, members of the crew felt that, in contrast to 1953, they were not "rowing together" and the group had evidently failed to achieve effective integration of individual differences. The race was won in 1953 and lost in 1954.

REFERENCES

1. Thorn, G. W.; Jenkins, D., and Laidlaw, J. C.: The Adrenal Response to Stress in Man, Recent Progr. Hormone Res. **8**:171, 1953.

2. Thorn, G. W., and Laidlaw, J. C.: Studies on the Adrenal Cortical Response to Stress in Man, Tr. Am. Clin. & Climatol. A. **65**:179, 1954.

3. Reddy, W. J.: Modification of the Reddy-Jenkins-Thorn Method for the Estimation of 17-Hydroxycorticoids in Urine, Metabolism **3**:489, 1954.

4. Renold, A. E.; Quigley, T. B.; Kennard, H. E., and Thorn, G. W.: Reaction of the Adrenal Cortex to Physical and Emotional Stress in College Oarsmen, New England J. Med. **244**:754, 1951.

5. Gray, S. J.; Ramsey, C. J., and Reifenstein, R. W.: Clinical Use of the Urinary Uropepsin Determinations in Medicine and Surgery, New England J. Med. **251**:835, 1954.

6. Lewis, J. L., Jr., and Thorn, G. W.: 17-Hydroxycorticoid Determinations in Sweat, J. Clin. Endocrinol. **15**:829, 1955.

7. Henneman, P. H.; Wexler, H., and Westenhaver, M. H.: A Comparison of Eosin-Acetone and Phloxine-Propylene Glycol Diluents in Eosinophil Counts, J. Lab. & Clin. Med. **34**:1017, 1949.

8. Jenkins, D.; Forsham, P. H.; Laidlaw, J. C.; Reddy, W. J., and Thorn, G. W.: Use of ACTH in the Diagnosis of Adrenal Cortical Insufficiency, Am. J. Med. **18**:3, 1955.

9. Drekter, I. J.; Heisler, A.; Scism, G. R.; Stern, S.; Pearson, S., and McGavack, T. H.: The Determination of Urinary Steroids: I. The Preparation of Pigment-Free Extracts and a Simplified Procedure for the Estimation of Total 17-Ketosteroids, J. Clin. Endocrinol. **12**:55, 1952.

10. Holtorff, A. F., and Koch, F. C.: The Colorimetric Estimation of 17-Ketosteroids and Their Application to Urine Extracts, J. Biol. Chem. **135**:377, 1940.

11. Bucher, G. R.: Uropepsin: Review of Literature and Report of Some Experimental Findings, Gastroenterology **8**:627, 1947.

12. Anson, M. D., and Mirsky, I. A.: Estimation of Pepsin with Hemoglobin, J. Gen. Physiol. **16**: 59, 1943.

13. Lambert, G. F.: The Determination of Creatine and Creatinine, J. Biol. Chem. **161**:679, 1945.

14. Cochran, W. G., and Cox, G. M.: Experimental Designs, New York, John Wiley & Sons, Inc., 1950.

15. Snedecor, G. W.: Statistical Methods, Ames, Iowa, The Iowa State College Press, 1946.

16. Klopfer, B., and Kelley, D. M.: The Rorschach Technique, New York, Yonkers-on-Hudson, 1946.

17. Harrower-Erickson, M. R.: Directions for Administration of the Rorschach Group Test, Rorschach Res. Exch. **5**:145, 1941.

18. Murray, H. A., and the staff of the Harvard Psychological Clinic: Thematic Apperception Test Manual, Cambridge, Mass., Harvard University Press, 1943.

19. Venning, E. H., and Kazmin, V.: Excretion of Urinary Corticoids and 17-Ketosteroids in the Normal Individual, Endocrinology **39**:131, 1946.

20. Pincus, G.; Romanoff, L. P., and Carlo, J.: A Diurnal Rhythm in the Excretion of Neutral Reducing Lipids by Man and Its Relation to the 17-Ketosteroid Rhythm, J. Clin. Endocrinol. **8**: 221, 1948.

21. Staehelin, D.; Labhart, A.; Froesch, R., and Kagi, H. R.: The Effect of Muscular Exercise and Hypoglycemia on the Plasma Level of 17-Hydroxysteroids in Normal Adults and Patients with the Adrenogenital Syndrome, Acta Endocrinol., to be published.

22. Ciba Foundation Colloquia on Endocrinology: Vol. 8. The Human Adrenal Cortex, edited by G. E. W. Wolstenholme and M. P. Cameron, Boston, Little, Brown & Company, 1955.

23. Hellman, L.; Bradlow, H. L.; Adesman, J.; Fukushima, D. K.; Kulp, J. L., and Gallagher, T. F.: The Fate of Hydrocortisone-4-C^{14} in Man, J. Clin. Invest. **33**:1106, 1954.

24. Herrick, R. F.: Red Top: Reminiscences of Harvard Rowing, Cambridge, Mass., Harvard University Press, 1948.

25. Freud, S.: Group Psychology and the Analysis of the Ego, London, The International Psycho-Analytical Press, 1922.

26. Rizzo, N. D.; Fox, H. M.; Laidlaw, J. C., and Thorn, G. W.: Concurrent Observations of Behavior Changes and of Adrenocortical Variations in a Cyclothymic Patient During a Period of 12 Months, Ann. Int. Med. **41**:4, 1954.

Treatment of Chronic Granulocytic Leukemia with Myleran

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In the hope of finding a less toxic analogue of nitrogen mustard, Haddow replaced the methyl groups in the nitrogen mustard molecule with various aromatic radicals. The compounds which were synthesized were not as effective as nitrogen mustard. Since the effect of nitrogen mustards is thought to be related to its ability to alkylate (i. e., exchange its halogen radical for some unknown body constituent), Timmis substituted another alkylating radical, sulfonic acid ester, for the halogen group. He synthesized a series of disulfonic ester molecules having various carbon chains. The four and five carbon chains were found to be most effective against the Walker rat carcinoma 256.[1]

Galton first reported the effects of 1,4-bis (methylsulfonoxy) butane (Myleran) in human leukemia.* After two years of experience in 19 patients with chronic granulocytic leukemia he reported clinical improvement similar to that obtained with x-ray therapy. Myleran was not found to be effective in the treatment of acute leukemia or chronic lymphocytic leukemia. Resistance to Myleran occurred in three patients. Subsequently others have reported similar results.† During the past 14 months we have treated and evaluated 24 cases of chronic granulocytic leukemia with this drug.

METHOD

Among the 24 patients with chronic granulocytic leukemia who were treated with Myleran, 13 were females (Table 1) and 11 were males. Age range was from 2 to 72 years. Only two patients were under 20 years, and one was over 70 years of age. The duration of symptoms prior to Myleran therapy varied from two weeks to four years. Eight patients received other forms of antileukemic therapy prior to receiving Myleran. Six patients received courses of both urethan and x-ray therapy. Two received only one course of urethan.

TABLE 1.—*Patients with Chronic Granulocytic Leukemia Treated with Myleran*

	Av.
Patients, no.	24
Age, yr.	44 (2-72)
Sex	13 females
Duration of symptoms, mo.	13 (0.5-48)
Previous treatment	**Patients, No.**
Urethan	2
Urethan and x-ray	6

The diagnosis of chronic granulocytic leukemia was established by the usual clinical and laboratory findings. All patients with chronic granulocytic leukemia who were seen after March 1, 1954, received Myleran except those who were already receiving and responding to other forms of management. The clinical findings, hemoglobin, and leucocyte and differential counts were observed at weekly intervals until a maintenance dose could be established, after which the patients were seen semi-

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From the Hematology Section of the Department of Medicine, University of Illinois, College of Medicine. Technical assistance was given by Adelle M. Frost.

* References 2 and 3.

† References 4-9.

monthly. All of the patients were treated in the office or as outpatients in the hematology clinic.

Bone marrow aspirations were obtained before Myleran therapy and again after leucocyte counts were within normal range.

TABLE 2.—*Dosage Schedule of Myleran in Patients with Chronic Granulocytic Leukemia*

	Av.	Range
Initial dose, mg./day	7	4-14
Required to lower WBC to normal		
Total dose, mg.	259	70-534
Time, wk.	6.2	3-12
Maintenance dose, mg./day	1.5	3-4
Duration of therapy, mo.	6	3-13
Duration of remission, mo.	4.5	1-12
Number of relapses per patient	0.75	0-5

RESULTS

DOSAGE SCHEDULE AND THE WHITE CELL COUNT (TABLE 2)

A. Initial Dosage.—The initial dose of Myleran depended upon the height of the leucocyte count. Patients with counts greater than 100,000 cells/cu. mm. received 8 to 10 mg/day; those with counts between 50,000 and 100,000 received 6 to 8 mg/day, and those with counts less than 50,000 received less than 6 mg/day. Reduction in the leucocyte count occurred during the first two weeks of therapy. The initial dose was reduced according to the rate at which the white cell count decreased. If the white cell count gradually decreased, then the initial dose was maintained until the leucocyte count was in the vicinity of 15,000/cu. mm., at which time maintenance dosage was established. Sensitivity to Myleran varied from patient to patient. Some patients were more sensitive to Myleran than others. In three patients precipitous drops (94%, 51%, 66%) in the leucocyte count occurred after one week of therapy. When this occurred, the dosage was reduced accordingly or was discontinued.

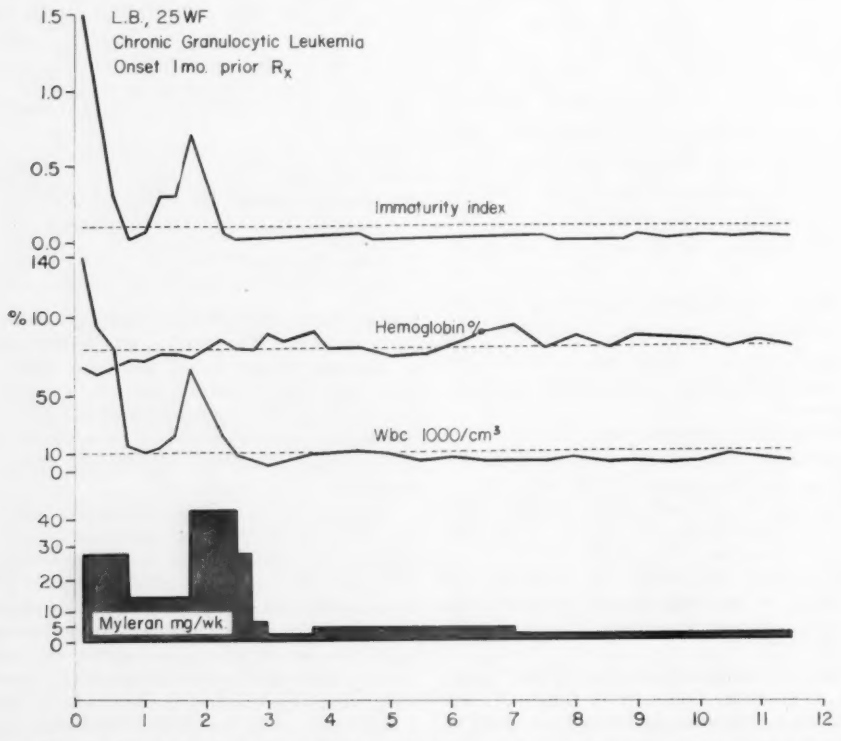


Fig. 1.—Chart showing a favorable hematologic course in a patient with chronic granulocytic leukemia treated with Myleran.

The white cell counts were reduced to normal levels (i. e., < 12,500/cu. mm.) in all of the patients after 3 to 12 weeks of therapy, with use of total doses ranging from 70 to 534 mg. Leucopenia (i. e., WBC < 3500 cells/cu. mm.) occurred in three patients receiving Myleran. White cell counts became elevated again as soon as the agent was discontinued in all of the leucopenic patients.

B. Maintenance Dosage.—A maintenance dose was established as soon as the white cell count approached normal range. The dosage varied with the individual patient and ranged from 2 mg/week to 4 mg/day. Maintenance dose (Fig. 1) was determined as the smallest amount of Myleran necessary to prevent elevation or further reduction in the white cell count. Two patients did not receive maintenance therapy and maintained normal counts for one and six months, respectively.

Dosage and Relapse

To date seven patients have relapsed. Five patients relapsed once; one patient, twice, and one, five times. All responded to a subsequent course of Myleran. The dosage schedule was similar to the initial schedule in all except the patient who relapsed five times. In this patient each subsequent relapse has required higher doses of Myleran (Fig. 2). The last relapse required 14 mg/day for two weeks before the white cell count became normal. The relapse rate, to date, is 0.75 relapses per patient.

Duration of Remission

A patient was considered in remission whenever he was clinically asymptomatic,

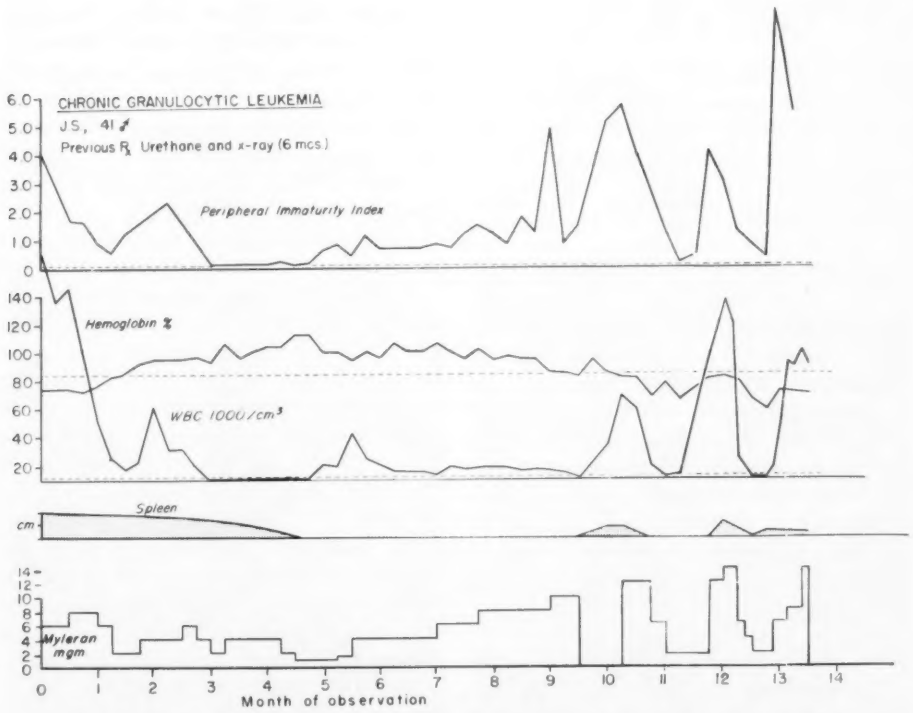


Fig. 2.—Chart showing hematologic relapses and subsequent response to further therapy with Myleran in a patient with chronic granulocytic leukemia. Each subsequent remission was of shorter duration, and each relapse required larger doses of Myleran.

the leucocyte count was less than 12,500, the differential count or the peripheral immaturity index was normal, and the hemoglobin level and the bone marrow were normal. The degree of remission, therefore, varied with the patient. However, all patients met the criteria for remission except two who remained anemic. At the present time the durations of remission have ranged from 1 to 13 months (mean, 4.5 months).

Clinical Effects

Subjective improvement was noted in all of the patients treated. Increase in the feeling of well-being and amelioration of malaise and loss of energy were prominant features, which appeared to be independent of the hematologic improvement. Weakness and fatigability, however, decreased as the degree of anemia decreased. Otitis media, rhinitis, or sinusitis were troublesome complications which resisted antibiotic and other conventional otolaryngologic therapeutic measures. Symptoms from these complications persisted until the white cell count became normal.

Table 3.—*Effect of Myleran upon the Spleen*

Patients, No.	Size of Spleen*	
	Before Therapy	After Therapy
11	(4-20)	0
3	4, 10, 20	2, 5, 6

* Measured as centimeters below the left inferior costal margin at the midclavicular line.

Table 4.—*Peripheral Blood Changes in Chronic Granulocytic Leukemia Treated with Myleran*

	Prior to Therapy	Early Remission
Hemoglobin, gm.	10.9 (7.5-14.4)	13.2 (10.0-17.5)*
WBC, 1000/cm.^{3}	155.2 (400.0-33.0)	8.0 (5.0-12.5)*
Immaturity index	2.6 (5.6-0.4)	0.4 (1.4-0)*

* Difference highly significant ($P < 0.001$); values within parentheses indicate range.

Spleen and Liver

Splenomegaly was found in 14 patients. The position of the tip of the spleen varied from 2 to 20 cm. below the inferior costal margin at the midclavicular line. During remission (Table 3) the tip of the spleen was no longer palpable in any but three patients. In these patients the tip of the spleen was less than half the initial distance. Enlargement of the spleen recurred with relapse and subsequently subsided with remission.

Hepatomegaly (2 to 8 cm. below the right costal margin in the midclavicular line) was present in seven patients. The liver was no longer palpable in six after remission.

Hematological Changes (Table 4)

Leucocyte counts initially ranged from 33,000 to 400,000/cu. mm. (mean, 155,000). The average white cell count during remission was 8000/cu. mm. (range, from 5000 to 12,500), which represented a significant ($P < 0.001$) reduction in all of the patients treated. By the end of the first week of therapy white cell counts were reduced by 10% to 60%.

Hemoglobin values before treatment ranged from 7.5 to 15.5 (mean, 10.0) gm/100 ml. Thirteen patients were anemic prior to therapy. Anemia was corrected in all except two patients. During remission, hemoglobin values ranged from 10.0 to 17.5 (mean, 10.9) gm/100 ml. This represents a significant elevation ($P < 0.001$).

The peripheral immaturity was expressed as a numerical index calculated from the ratio of immature granulocytes to segmented granulocytes. Normally this index is less than 0.1. Previous to therapy this index averaged 2.6, ranging from 5.6 to 0.4. During remission the mean peripheral blood immaturity index was 0.4 and ranged from 1.4 to 0, which was also a highly significant reduction ($P < 0.001$). The peripheral immaturity index closely paralleled the changes in the white cell count. In some patients a relapse was heralded by an increase in this index (left shift). In the patient who developed acute leukemia the peripheral blood showed progressive increase in this index, associated with the increasing number of blast cells (Fig. 2).

The differential blood cell count was significantly altered in all of the patients treated.

In 7 of 12 patients the peripheral blood did not show any evidence of a leukemic process during remission. In two patients (Fig. 3) a completely normal differential count persisted for 10 months. In all the patients reduction in the white cell count was accompanied by a reduction in the number of blasts and other immature cells. One patient on maintenance therapy showed progressive increase in the number of immature cells even though the white cell count remained normal. In this patient, when Myleran was discontinued a prompt rise in the cell count occurred (Fig. 2). The immaturity index and leucocyte count were subsequently reduced, after a second course of Myleran.

Basophilia and eosinophilia occurred in most of the patients during and shortly after the period of white cell count reduction. However, the increased percentage of basophiles and eosinophiles was relative. When the absolute numbers of basophiles and eosinophiles are plotted (Fig. 4), an actual reduction in the number of these cells is found.

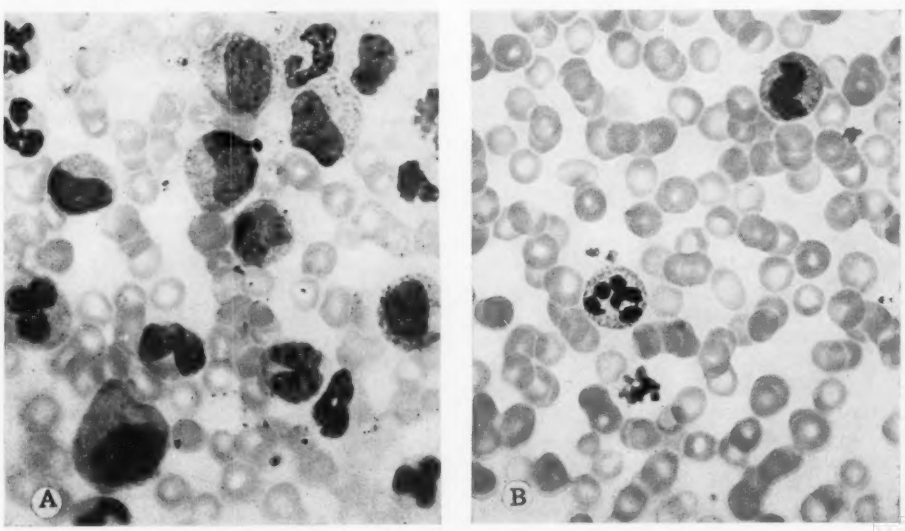
The blood platelets (Table 5) were evaluated in the stained peripheral smear. Eight patients did not show any marked alteration in their platelets. Platelets appeared increased in four, reduced in one, and were increased early in the course of therapy and later reduced in two. The increase in platelets was most pronounced during the early phase of remission. Thrombocytopenia was not observed in any of the patients treated.

TABLE 5.—*Changes in the Number of Platelets Observed on Direct Smears*

Platelets	Patients	
	No.	Per Cent
No effect	8	38
Increased	4	19
Decreased	1	5
Increase/decrease	2	9
Unknown	6	29

Bone marrows prior to therapy contained a marked granulocytic and megakaryocytic hyperplasia, with relative reduction in erythropoiesis. Granulocytic hyperplasia was substantially reduced in bone marrows obtained during remission. In no instances were normal bone marrows (i. e., without some degree of granulocytic hyperplasia) found during remission.

Fig. 3.—Peripheral blood in a patient with chronic granulocytic leukemia before (*A*) and after (*B*) treatment with Myleran.



Clinical Outcome to Date

Up to this time five patients have died while on Myleran therapy.

Case 1.—A 35-year-old white woman died two years after the onset of her leukemic symptoms. She received a total dose of 196 mg. of Myleran over a six-week interval. Three weeks before her death a fever developed. Her white cell count at this time was 23,800/cu. mm. The dose of Myleran was raised from 2 mg/day to 4 mg/day. One week later Myleran therapy was discontinued because her leucocyte count decreased to 1450 cells/cu. mm. Blood cultures at this time grew out Pseudomonas aeruginosa. The patient was hospitalized and given

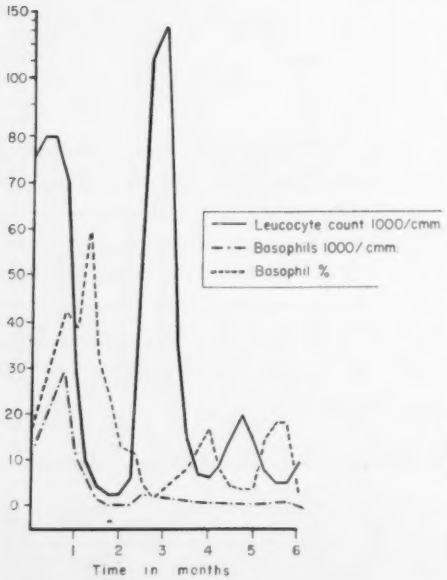


Fig. 4.—Graph shows the relationship of the percentage of basophiles and absolute numbers of basophiles to the white cell count.

antibiotics. Seven days later the white cell count further decreased to 700/cu. mm., with 80% blast cells. The patient died the next day. Postmortem examination revealed an overwhelming Pseudomonas septicemia.

Case 2.—A 54-year-old white woman died four years after the onset of her leukemic symptoms. Prior to Myleran she received courses of x-ray therapy and urethan. She was given Myleran for the first time 11 weeks before she died. After a total dose of 126 mg. of Myleran, given over a three-week period, the white cell count was reduced from 64,000 to 5300/cu. mm. No maintenance therapy was given. Subsequently, the white cell count gradually increased to 16,000/cu. mm. three weeks prior to death. The patient was given 2 mg/day of Myleran for one week. The dose was then raised to 6 mg/day because the leucocyte count rose to 55,000/cu. mm. Three days before death the dose of Myleran was increased to 8 mg/day, since the leucocyte count was then 79,000/cu. mm. The patient died suddenly. Postmortem examination revealed a cerebral vascular accident to be the cause of death.

Case 3.—A 47-year-old white woman had symptomatology of chronic granulocytic leukemia of 40 months' duration. She had previously received urethan for two years until the leukemic process became resistant to further therapy. Subsequently, an eight-month course of x-ray therapy to the spleen resulted in some improvement, although the anemia, leucocytosis, and granulocytic immaturity persisted. She then received 200 mg. of Myleran over a seven-week interval. The white cell count decreased from 64,000 to 9700/cu. mm., and the degree of peripheral immaturity also decreased (peripheral immaturity index decreased from 0.6 to 0.3). During the sixth week of therapy the patient developed fever, chills, and night sweats. She was hospitalized by her private physician and treated with antibiotics, blood transfusion, and other supportive measures. Her fever persisted until her death, nine weeks after initiation of Myleran therapy. The cause of death was not determined.

Case 4 (Fig. 5).—A 24-year-old white woman had had symptoms from chronic granulocytic leukemia for two years. Prior to Myleran she received a course of urethan followed by a course of x-ray therapy given over a twenty-month interval. She was given 280 mg. of Myleran over a six-week period. The white cell count decreased from 80,000/cu. mm. to 4200/cu. mm. and was associated with a rise in hemoglobin and almost complete normalization of the peripheral blood. She maintained a normal white cell count for three weeks, during which time maintenance therapy was not given. During the 10th week the white cell count increased, and the patient required a second course of Myleran; total dose was 196 mg. given over a five-week interval. The white cell count decreased from 110,000 to 7200 and was associated with comparable reduction in the anemia and granulocytic immaturity. Maintenance therapy varied from 4 mg/week to 6 mg/day. The number of blast cells in the peripheral blood and anemia progressively increased despite the normal white cell count. During the 24th week of therapy, 6-mercaptopurine (100 mg/day) was given to the patient in the hope of reducing the number of blast cells. Myleran was discontinued on the 26th week, the patient receiving only 6-mercaptopurine

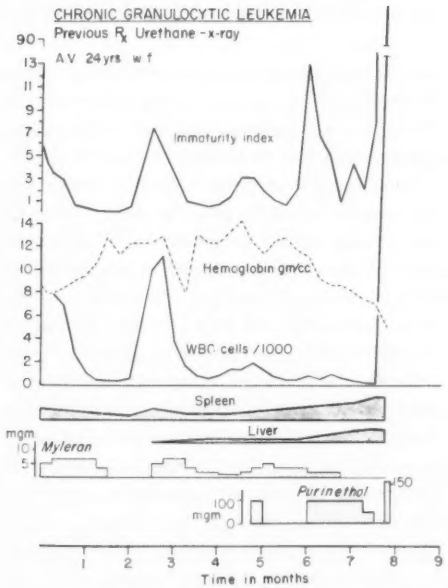
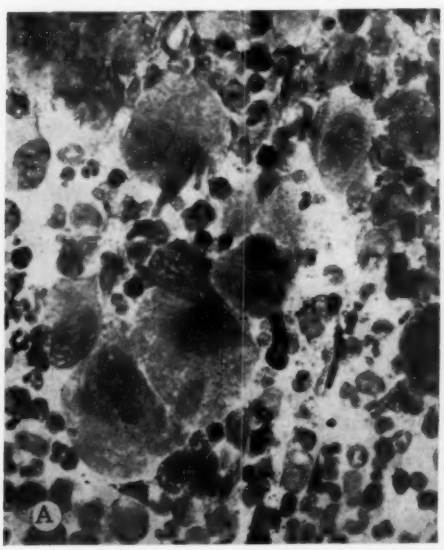


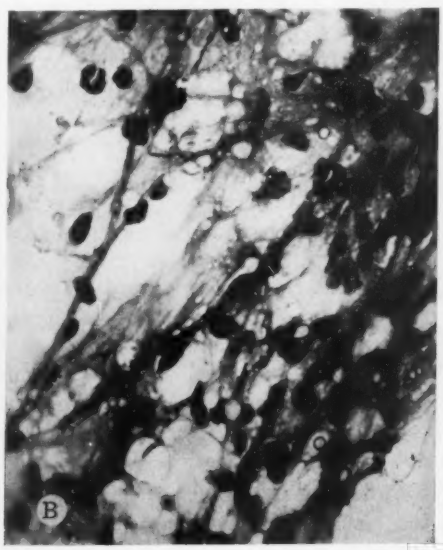
Fig. 5.—The hematologic course in a patient with chronic granulocytic leukemia treated with Myleran. Graph shows the initial response, followed by subsequent relapse, and gradual conversion into acute leukemia, which terminated in death.

until the 30th week. At this time the white cell count was 1250/cu. mm., with 31% blast cells, 14% immature granulocytes, 6% segmented neutrophiles, 4% eosinophiles, 4% basophiles, 21% lymphocytes, and 20% monocytes. All therapy was discontinued, since no real improvement occurred with 6-mercaptopurine. When the patient returned the following week the white cell count was 285,000/cu. mm., with 97% blast cells and 3% eosinophiles. The patient again was given 6-mercaptopurine, 200 mg/day; however, she died three days after her last clinic visit, from her acute leukemia.

Case 5.—An 18-year-old white woman had had symptoms from chronic granulocytic leukemia for only one week before she received Myleran. This patient was seen in consultation by one of us (L. R. L.), who recommended that she receive Myleran. The patient improved dramatically, the white cell count decreasing from 400,000/cu. mm. to normal range in approximately six weeks, after which she was given maintenance therapy of 2 mg/day. The patient failed to return to her family physician at the appointed intervals. After 10 weeks of maintenance therapy she returned to her physician with symptoms of sore throat, weakness, fever, and prostration. The hemoglobin at this time was 4.0 gm/100 ml., with a leucocyte count of 700/cu. mm. and differential count of 97% lymphocytes and 3% segmented neutrophiles. Platelets were absent from the blood smear. Bone marrow smear showed complete aplasia (Fig. 6), absence of all normal hemopoietic elements, increased fibrous tissue, plasma cells, and reticular elements. The patient suddenly died on the following day.

Fig. 6.—Bone marrow before (*A*) and after (*B*) the development of a Myleran-induced pancytopenia in a patient with chronic granulocytic leukemia receiving unsupervised therapy.





Side-Effects

Serious drug toxicity was not observed in any patient who received careful management with Myleran. Gastroenteropathy, skin reactions, or other drug reactions were not observed. The one patient who developed marrow aplasia from the agent did so in the absence of carefully supervised drug administration. The fact, however, remains that this agent is capable of causing marrow aplasia.

All of the four female patients who were treated for more than three months developed amenorrhea. The endometrium, on biopsy, was found to be hypoplastic. At time of writing the menstrual periods have not returned in any of the amenorrheic females.

Comment

Myleran appears to be a valuable addition to the antileukemic armamentarium. Since other workers have reported Myleran to be ineffective in other forms of leukemia, we have limited the use of this agent to patients with chronic granulocytic leukemia. Our results are similar to published and unpublished observations of other investigators.

Reduction in the leucocyte count is a prominent feature. The leucocyte count in all of our patients was reduced to normal levels. Some investigators, however, do not attempt to reduce the leucocyte count to normal levels, but gauge their dosage by the clinical response and hemoglobin level. Wilkenson [9] feels that this method minimizes the danger of marrow suppression. The rate and magnitude of reduction in the leucocyte count depends upon the daily dose and the sensitivity of the leukemic process to the agent. Small doses of Myleran given over prolonged intervals will reduce the leucocyte counts to normal levels, whereas large doses result in more dramatic responses. Patients who received other forms of antileukemic therapy previously responded to Myleran in a manner comparable to those who did not receive prior therapy. Cross resistance to Myleran does not appear to occur.

We have not had the opportunity to confirm Galton's impression that patients receiving Myleran become resistant to radiotherapy.[10]

Whether continuous or interrupted therapy is used depends on the individual situation. Nearly all our patients required maintenance therapy in order to sustain normal leucocyte counts. Only one patient in this series did not require maintenance therapy. Maintenance doses should be given when white cell counts can not be maintained at normal levels without therapy. Myleran does not seem to have cumulative effects. Discontinuation of therapy prevents further leucocyte count reduction. This is an advantage of Myleran over other forms of antileukemic agents, for it allows closer control of therapy. The rapid responsiveness of the disease to changes in dosage has also been observed by others.

Resistance to Myleran occurs in approximately 13% (0% to 36%) of the patients reported in the literature.‡ This is obviously an underestimate of the ultimate percentage of resistant cases. However, it does give a crude guide for therapeutic prognostication during the early phase of therapy. We have not observed the development of complete resistance to Myleran. Relapses did not require larger total doses except for one patient (Fig. 2). Similar findings have been observed by Galton.[10] In this series, however, subsequent remissions were of shorter duration than the initial remission. Resistance to Myleran developed in three patients of Galton's series. All three patients were in the group receiving large doses of Myleran. He intimates a possible relationship between large doses and the development of resistance.

The normalization of the leucocyte differential count in many of the treated patients has been confirmed in other reports. The percentage of patients in whom this can be expected cannot be determined, since the actual figures are not reported. The close correlation between the peripheral blood immaturity index and the leucocyte count is an interesting finding. In some patients increase in this index heralded a forthcoming relapse.

‡ References 4-10 and present series.

Acute exacerbation has occurred in 12 of 140 patients reported in the literature.§ The development of the acute phase does not appear to correlate with the amount, or duration, of Myleran therapy or with the duration of the disease. It is our impression that this occurrence of acute exacerbation is the same as would naturally be expected with other forms of therapy. Therefore, the existing evidence does not appear to support the fears that Myleran may induce acute exacerbation of the disease process. It is interesting to note in three patients that the number of blast cells increased in the blood without concomitant increases in the leucocyte count.

Approximately one-fourth of the reported cases have died while receiving Myleran, during an interval of one to four years.

The increase in the percentage of basophiles and eosinphiles during and shortly after the period of white cell count reduction was relative. When the differential counts were compared with the absolute numbers, an actual decrease in the number of basophiles and eosinophiles was found. This discrepancy appears to be due to the slower rate of decrease in the basophiles as compared with the other granulocytes.

Thrombocytopenia did not occur in any of the patients we have treated. Thrombocytopenia complicating therapy is reported and is related to the size of the dose used.‖ The increase in platelets found in some of the patients is of interest. This phenomenon is reported in the literature.

Correction of the anemia is a prominent feature of Myleran therapy and is confirmed by other reports. This effect reduces the necessity for transfusions. Transfusions should only be given to those patients failing to respond to therapy. A failure of anemia to improve with Myleran therapy appears to represent an ominous prognosis.

The beneficial effects of Myleran on the size of the liver and spleen have been confirmed in other reports. In Wilkenson's group reduction in the size of the spleen was not as marked.[9] This is probably due to the difference in dosage. Recurrent splenomegaly with relapse also responds to subsequent therapy.

The amenorrhea appears to be related to Myleran therapy. In Galton's group amenorrhea occurred in one of the two female patients who were under 40.[10] This effect may be due to the action of Myleran upon either the endometrium or the ovaries. Androgenic-estrogenic determinations on the blood and urine were not performed. It appears that only 4 patients of the 140 reported in the literature developed serious hemopoietic side-effects.¶ We have observed one patient who developed aplastic myelopoiesis. Report of this death should not detract from the value of this agent, since death may occur from misuse of any drug. This patient exemplifies the outcome which may result from administration of agents without adequate observation and supervision. If any therapy is to be of value, close observation is of paramount importance. Patients receiving Myleran in doses of 2 to 10 mg/day should have weekly hemoglobin determinations and leucocyte counts. When the dose is reduced to less than 2 mg/day these determinations may be performed at semimonthly intervals. Patients receiving more than 10 mg/day should have semiweekly hemograms. A patient should receive a supply of medication sufficient only for the interim of follow-up visits. When all these precautions are taken into account, Myleran appears to be a relatively safe antileukemic drug when its use is compared with the other available antileukemic regimens. Whether or not Myleran will be the drug of choice in treatment of this disorder depends on several factors which remain to be determined: (1) the frequency with which resistance to the agent develops; (2) the effect on the life expectancy; (3) the effect on the total clinical course of the disease.

SUMMARY AND CONCLUSION

The clinical and hematologic effects of 1,4-bis (methylsulfonoxy) butane (Myleran) were studied in 24 patients with chronic granulocytic leukemia who were treated for

§ References 4-10 and present series.

‖ References 2 and 3.

¶ References 2-4 and 9.

periods ranging from 1 to 13 months. Leucocyte counts were reduced to normal levels initially in all the patients. The degree of peripheral immaturity paralleled the changes in the white cell count. Relative disproportion in the percentage of these elements occurs during active white cell count reduction, owing to the difference in the rate of reduction. All stages of granulopoiesis in the peripheral blood are decreased with Myleran therapy. Improvement in subjective symptoms, anemia, and hepatosplenomegaly were prominent features.

Amenorrhea occurring in four young women was associated with endometrial atrophy. Five patients died during therapy from the complications of chronic granulocytic leukemia. One patient receiving unsupervised therapy died from a drug-induced hemopoietic aplasia. The importance of closely supervised therapy is discussed. Myleran appears to be an effective agent in producing temporary remission in chronic granulocytic leukemia. Its effectiveness varies with the patient treated. It has some advantage over existing forms of therapy, including ease of administration, absence of cumulative effect and side-effects, and close control of response. Results with Myleran therapy appear similar to those obtained from x-ray. The effect of Myleran on the life expectancy of the patient with chronic granulocytic leukemia is not yet known.

ADDENDUM

Since this article was submitted we have treated 8 more patients with Myleran, making a total of 32 patients. The hematological and clinical findings have been similar to the results reported in this paper. Two of the original patients showed good response to subsequent x-ray therapy, contrary to what has been reported.[10]

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REFERENCES

1. Haddow, A., and Timmis, G. M.: Myleran in Chronic Myeloid Leukæmia, Lancet **1**:207 (Jan. 31) 1953.

2. Galton, D. A. G.: Myleran in Chronic Myeloid Leukæmia, Lancet **1**:208, (Jan. 31) 1953.

3. Galton, D. A. G.: Chronic Granulocytic Leukæmia, Brit. J. Radiol. **26**:285, (June) 1953.

4. Wintrobe, M. M.; Cartwright, G. E.; Fessas, P.; Hout, A., and Altman, S. J.: Chemotherapy of Leukemia, Hodgkin's Disease and Related Disorders, Ann. Int. Med. **41**:447 (Sept.) 1954.

5. Petrakis, N. L.; Bierman, H. R.; Kelly, K. H.; White, L. P., and Shimkin, M. D.: The Effect of 1,4 Dimethanesulfonoxybutane (G. T. 41 or Myleran) upon Leukemia, Cancer **7**:383 (March) 1954.

6. Levin, W. C.; Thaddeus, A. P.; Vaughan, J. R., and Tsai, S. Y.; Experience with 1,4 Dimethanesulfonoxybutane (Myleran) in the Treatment of Chronic Myelocytic Leukemia, J. Lab. & Clin. Med. **44**:890 (Dec.) 1954.

7. Bollag, W.: Therapeutische Erfahrungen, Schweiz. med. Wchnschr. **83**:872 (Sept. 12) 1953.

8. Hansen, P. B., in Ciba Foundation Symposium on Leukæmia Research, edited by G. E. W. Wolstenholme and M. P. Cameron, Boston, Little Brown & Company, 1954, p. 205.

9. Wilkenson, J. F., in discussion on the Chemotherapy of the Reticuloses, Proc. Roy. Soc. Med. **46**:685 (Sept.) 1953.

10. Galton, D. A. G., and Till, M.: Myleran in Chronic Granulocytic Leukæmia, Lancet **1**:425 (Feb. 26) 1955.

Subacute Bacterial Endocarditis

Splenectomy in Cases Refractory to Antibiotic Therapy

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With the use of modern antibiotic therapy, 60% to 70% of patients with subacute bacterial endocarditis are cured. Formerly at least 97% of cases were fatal.[1] Even if penicillin or other antibiotics are temporarily successful in sterilizing infected heart valves, a "focus" of infection in any organ of the body may "shower" bacteria into the blood to prevent permanent cure.

The literature contains few reports of cases in which removal of the spleen, the site of an infected infarct or abscess, resulted in cure of the disease. Riesman,[2] in 1918, suggested that the spleen might serve as a "focus" of infection in certain cases of subacute bacterial endocarditis. Polowe,[3] in 1939 reported a case of subacute bacterial endocarditis in which a 20-month cure followed splenectomy; in his survey of the literature prior to that year, he found 15 fatal cases of this disease recorded in which splenectomy had been performed.

In recent years European reports have suggested that the spleen may be responsible for the continued bacteremia in this disease. Fellinger and Weissel,[4] in 1952, described 11 patients in whom the diagnosis of subacute bacterial endocarditis had been established by culturing the bacteria from the blood. The disease persisted in these patients despite antibiotic therapy. Splenectomy was performed in each of the 11 patients, but sustained remissions occurred in only 5. Giraud[5] and associates, of Paris, have reported three cases of antibiotic-refractory bacterial endocarditis in which sustained and increasing splenomegaly was a troublesome manifestation. Apparent cure followed splenectomy in all three cases. These authors recommend splenectomy for patients who are resistant to antibiotic therapy and for those in whom residual splenomegaly and/or progressive hemolytic anemia are present.

Of the cases of subacute bacterial endocarditis seen at the Indiana University Hospitals since 1946, three patients have received splenectomies after failure with antibiotic therapy alone.

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From the Departments of Pathology (Drs. Lingeman and Smith), Surgery (Dr. Battersby), and Medicine (Dr. Behnke) of the Indiana University School of Medicine and the Indiana University Medical Center.

REPORT OF CASES

CASE 1.—In September, 1946, a 27-year-old housewife was referred to the Indiana University Medical Center Hospitals. A diagnosis of subacute bacterial endocarditis had been established at another hospital. The patient presented a history of typical rheumatic fever at the age of 9 and chorea at 11 years and had first become aware of "heart trouble" at the age of 12. Her two living children were aged 9 years and 17 months, respectively. Five months prior to admission chills and fever followed a self-induced abortion. Only temporary relief followed sulfonamide and penicillin therapy, and the symptoms returned. During the two weeks prior to admission to the University Hospitals, she had received 1,000,000 units of penicillin daily, after streptococci of the viridans type had been identified in blood cultures.

Upon admission the patient was acutely ill, had a temperature of 98 F, a pulse rate of 70 per minute (regular), and a blood pressure 120/80 mm. Hg. Petechiae were noted on the skin of the anterior chest wall. The lungs were normal. The heart was not enlarged. A Grade 3 systolic and a Grade 2 early diastolic murmur were heard over the mitral area, with accentuation of the first sound. The abdomen was essentially normal; the spleen was not

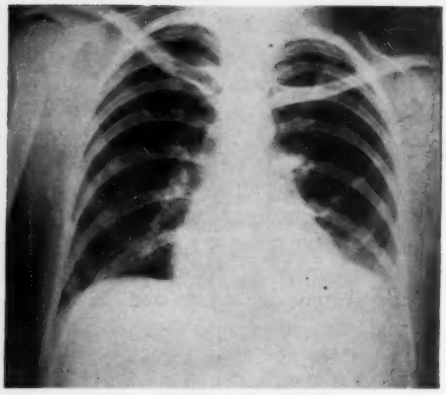

Fig. 1 (Case 1).—Posteroanterior roentgenogram of chest, showing elevation of the left diaphragm with accompanying pleural reaction.

palpable. A Streptococcus of the viridans type was isolated from the blood.

In spite of penicillin therapy up to 10,000,000 units per day, the temperature rose daily, sometimes to 103 F. On Nov. 20 severe pain developed in the left upper quadrant of the abdomen and large doses of morphine were required for relief. Dullness to percussion was elicited over the anterior portion of the left chest (Fig. 1). The spleen was not palpable at any time.

Splenectomy was performed Nov. 30, 1946. The spleen was adherent to the diaphragm, stomach, colon, and lateral abdominal wall, but it was removed without unusual difficulty.

After splenectomy a daily dose of 10,000,000 units of penicillin was continued for seven weeks, during which time blood cultures were negative. The patient was dismissed from the hospital approximately four months after her admission, symptom-free.

She returned to the cardiac clinic at regular intervals for three years after discharge. She was free of symptoms, and several blood cultures were negative. In 1953, after the birth of her third child, hysterectomy was performed because of chronic cervicitis and postpartum uterine bleeding. The postoperative course was uneventful. At the present time the patient is able to care for her three children and is symptom-free except for slight dyspnea upon exertion (Fig. 2).

Pathologic Report.—The spleen weighed 240 gm. and measured 14×8×5 cm. In the superior pole was a 5×3 cm. area of gray, necrotic material, from which a Streptococcus of the viridans type was cultured. The focus appeared microscopically as an area of necrosis in which only faint outlines of splenic architecture were visible. In the necrotic area were scattered polymorphonuclear leucocytes and some clumps and short chains of Gram-positive cocci. The area was surrounded by a zone of fibroblasts and some dense fibrous tissue. In the relatively intact surrounding tissue the sinusoids were prominant and there was an increase of fibrous tissue and lymphoid follicles.

Case 2.—A 22-year-old pregnant woman was readmitted to the Indiana University Medical Center Hospitals, Nov. 23, 1947, for the fifth time. She had suffered from typical rheumatic fever at the age of 14 years. At the age of 20 a diagnosis of subacute bacterial endocarditis had been made following isolation of streptococci of the viridans type from the blood. This infection had been apparently controlled by the administration of 2,400,000 units of penicillin daily for 20 days. During the four months preceding her fifth admission, she had experienced intermittent fever, chills, and malaise, all of which had followed an initial episode of "flu." Forty-eight hours before admission, hemorrhagic "spots" appeared on the skin accompanied by chills,

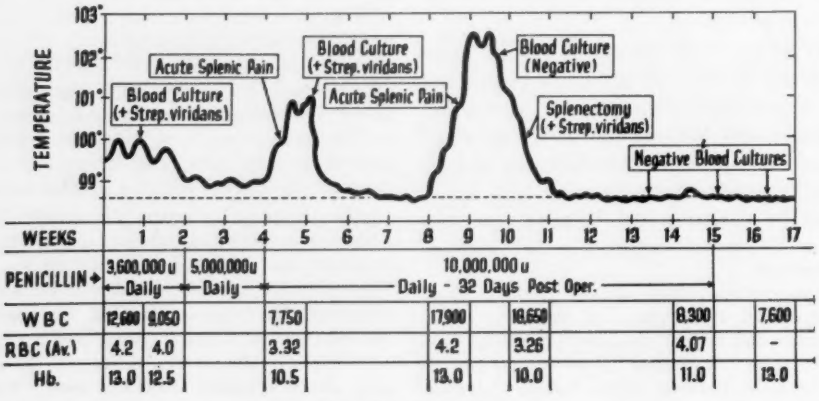
TEMPERATURE
103°
102°
101°
100°
99°
Blood Culture (+ Strep. viridans)
Acute Splenic Pain
Blood Culture (+ Strep. viridans)
Acute Splenic Pain
Blood Culture (Negative)
Splenectomy (+ Strep. viridans)
Negative Blood Cultures
WEEKS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
PENICILLIN → 3,600,000 u Daily 5,000,000 u Daily 10,000,000 u Daily - 32 Days Post Oper.
WBC 12,600 9,050 7,750 17,900 19,650 8,300 7,600
RBC (Av.) 4.2 4.0 3.32 4.2 3.26 4.07 -
Hb. 13.0 12.5 10.5 13.0 10.0 11.0 13.0

Figure 2 (Case 1)

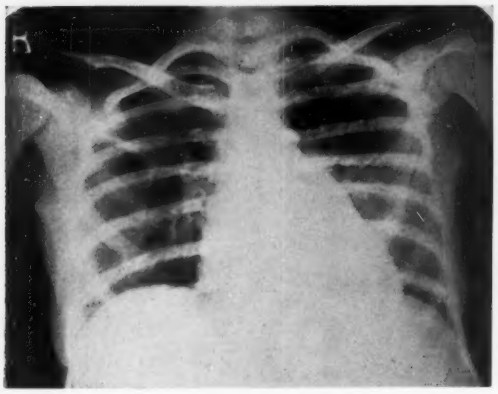

Fig. 3 (Case 2).—Posteroanterior roentgenogram of chest, showing generalized cardiac enlargement and pleural reaction in the left hemithorax.

fever of 104 F, and severe pain in the left upper quadrant of the abdomen.

The patient appeared chronically ill. She had a temperature of 102 F, a pulse rate of 100 per minute, and a blood pressure 110/78 mm. Hg. Petechiae were noted in the skin. The lungs were normal. The point of maximal impulse of the heart was 10 cm. to the left of the midsternal line. A systolic murmur, Grade 4, and a soft diastolic murmur, Grade 2, were heard over the mitral area. A Grade 2 diastolic murmur was heard over the aortic area. The spleen was palpable 6 cm. below the left costal margin. The uterus was enlarged to the size of a four-month gestation; fetal heart sounds were audible.

The patient experienced repeated episodes of severe left upper quadrant abdominal pain, which was referred to the left shoulder. Recurrences of petechiae accompanied intermittent low-grade fever. Three weeks after admission, a pleural friction rub was heard over the inferior portion of the left chest (Fig. 3).

Splenectomy was performed Dec. 18, 1947. The spleen was adherent to the pancreas, stomach, and diaphragm and contained numerous thin-walled foci having the gross appearance of abscesses, several of which were ruptured as the organ was mobilized. Before surgery was completed, the patient went into shock, but she responded to transfusion with whole blood.

Repeated blood cultures were negative. Four months after the splenectomy the patient was delivered of a full-term viable infant; the puerperium was complicated by severe hemorrhage ascribed to uterine atony.

The patient was readmitted to the University Hospitals in the years that followed, once for infectious hepatitis and once for tooth extraction. In 1950, streptococci of the viridans type were again isolated from the blood, but they disappeared after penicillin therapy. In August, 1952, when congestive heart failure appeared for the second time, the patient was given digitoxin 0.1 mg. daily and diuretics, to which she responded poorly. In September of the same year she was readmitted in severe congestive heart failure, and she died the following day (Fig. 4).

Pathologic Report.—The spleen measured 22 by 15 by 8 cm. The entire superior one-half of the organ was replaced by a large necrotic cavity filled with semiliquid material. An infarct, 4×5×6 cm., was present in the lower pole. Material from this focus was cultured, but no organisms grew. Microscopically, the well-defined areas of necrosis contained remnants of splenic architecture. Around the periphery were clumps of bacteria and scattered

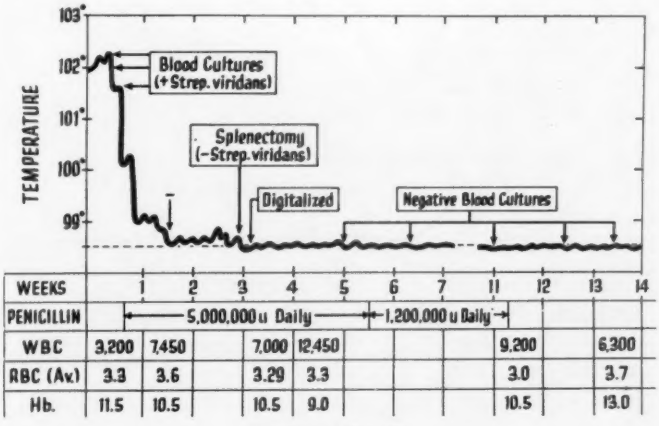

Figure 4 (Case 2)

polymorphonuclear leucocytes. A surrounding zone consisted of a layer of well-vascularized fibrous tissue. In the surrounding splenic tissue the sinusoids were prominent and there was an increase in fibrous tissue in some of the secondary follicles.

Autopsy Report.—The most impressive changes were noted in the heart, which weighed 450 gm. The visceral and parietal pericardia were densely adherent. The entire heart was dilated, and the wall of the left ventricle measured 15 mm. in thickness. The circumference of the ring of the mitral valve was 130 mm. The leaflets were slightly thickened by fibrous tissue, and there was minimal thickening of some of the chordae tendineae. Two minute calcified excrescences were noted, one on the atrial surface of the posterior leaflet and one on a chorda. The aortic ring measured 80 mm. The slightly thickened cusps were adherent at the commissures. The remaining valve rings were not abnormal. The heart showed no evidence of active rheumatic fever or of subacute bacterial endocarditis. The other organs were not remarkable except for evidence of chronic passive congestion in the lungs, liver, and kidneys and some healed infarcts in the right kidney. The brain was not examined. Microscopic sections confirmed the gross diagnosis of chronic valvular disease, with evidence of long-standing congestive heart failure.

CASE 3.—A 31-year-old machine operator was admitted to the Indiana University Medical Center Hospitals in August, 1952. He had suffered an attack of rheumatic fever, with typical migratory polyarthritis, at the age of 15 years and had failed a military induction examination at the age of 22 years because of "leakage of the heart." Following a tooth extraction, approximately six weeks prior to admission, he had noticed daily temperature elevation and extreme fatigue. On the day prior to admission he had experienced a sudden loss of consciousness.

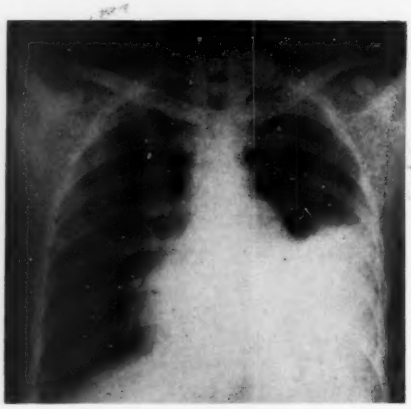

Fig. 5 (Case 3).—Posteroanterior roentgenogram of chest with large left pleural effusion.

On physical examination the patient was pale and chronically ill. There were no petechiae on the skin. The temperature was 103 F; the pulse rate was 90 per minute (regular), and the blood pressure was 110/62 mm. Hg. The lung fields were clear. The heart was not enlarged. A systolic murmur, Grade 3, was heard over the mitral area, with accentuation of the first sound and a clearly audible mid-diastolic click. No abdominal viscera were palpable. Both ankles were red, painful, and swollen. A Streptococcus, sensitive to chloramphenicol, was isolated from a blood culture. Other laboratory examinations were not abnormal. The admission x-ray examination of the chest was essentially normal.

Approximately 10 days after chloramphenicol therapy, 2 gm. per day, was initiated, the patient developed severe pain in the left shoulder and dull aching in the left upper quadrant of the abdomen. At this time there was dullness to percussion in the left chest inferiorly, accompanied by diminished

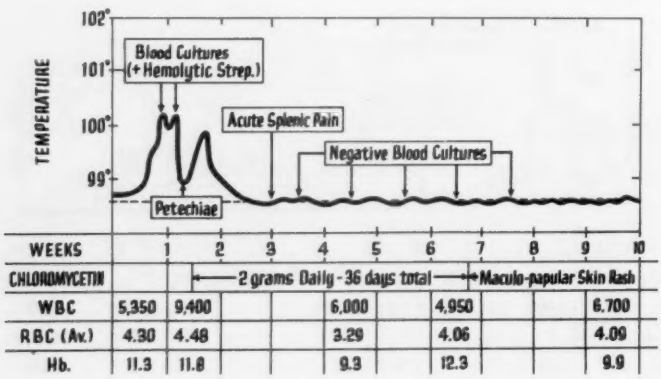

Fig. 6 (Case 3).—First admission.

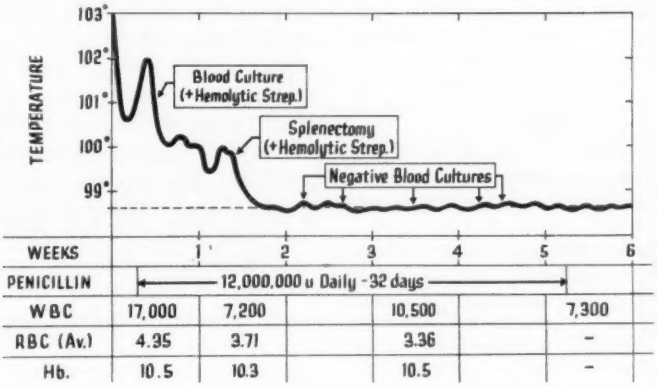

Fig. 7 (Case 3).—Second admission.

vocal and tactile fremitus. The spleen was not palpable. Fluoroscopic examination of the chest revealed diminished diaphragmatic excursion on the left, with the density of pleural effusion (Fig. 5). Fluid obtained by thoracentesis was cloudy; contained 4 gm. of protein per 100 ml. and 1275 leucocytes per cu. mm., 71% of which were lymphocytes, and proved to be bacteriologically sterile. Chloramphenicol therapy was continued, and the temperature returned to normal. The patient had no further pain. The pleural density seen on x-ray examination failed to resolve completely. The patient was discharged 23 days after cessation of the drug therapy (Fig. 6).

Nine days later, the patient was readmitted because of severe pain in the left anterolateral chest and recurrent chills and fever. In the 24 hours preceding admission he had coughed up approximately ½ pt. (about 250 cc.) of blood. At this time he was acutely ill and was coughing bloody semipurulent material. The cardiac murmurs had not changed. The spleen was not palpable, nor were petechiae observed. Antibiotic therapy was reinstituted, first penicillin and later streptomycin. The patient continued to have symptoms.

Splenectomy was performed Nov. 14, 1952. At surgery the spleen was firmly adherent to the diaphragm, stomach, and colon. During blunt dis-

Fig. 8 (Case 3).—Microscopic section of spleen showing an infarct. The necrotic area, right, with colonies of bacteria and inflammatory cells in the periphery, is well-demarcated from the relatively normal spleen by a layer of fibrous tissue.

section, approximately 300 cc. of necrotic material was released from a large cavity in the superior pole. The focus had extended through the splenic capsule, and the space entered was that of a subdiaphragmatic abscess from which an alpha-hemolytic Streptococcus was isolated.

The patient subsequently returned to full-time employment. He was seen in the out-patient cardiac clinic in August, 1953, and at the present time is able to work (Fig. 7).

Pathologic Report.—The spleen weighed 400 gm. and measured 11×4.5×13 cm. There was a large area of coagulation necrosis and a small healed infarct, 2.5×3×3 cm. In a microscopic section the necrotic tissue appeared as the eosinophilic, shadowy remnants of splenic structures; around the periphery there were bacterial colonies and scattered leucocytes, predominantly polymorphonuclear cells. There was an irregular surrounding zone composed of strands of fibroblasts, which in some areas were invading the necrotic focus. In the uninvolved splenic tissue the sinusoids were prominent and there was an increase of fibrous tissue (Fig. 8).

COMMENT

Splenomegaly is present in the majority of patients with subacute bacterial endocarditis. The common pathologic changes in these enlarged spleens are congestion, hyperplasia, and infarction. Despite rapid enlargement and the occurrence of large infarcts, pain in the left upper quadrant of the abdomen occurs infrequently. Spontaneous rupture is rare. Lockwood,[6] found only 10 cases reported prior to 1948.

Probably more often than is suspected, a splenic infarct becomes infected. The necrotic material, protected by a capsule of granulation or fibrous tissue, is excellent culture medium for bacteria; antibiotics even in high blood levels apparently cannot penetrate the "barrier" to eradicate the "focus."

Each of the three patients presented in this paper had typical subacute bacterial endocarditis, severe pain in the left upper quadrant of the abdomen, and continuous bacteremia in the presence of high blood levels of antibiotics. At some time during the preoperative course of each patient there was evidence of pleural reaction or fluid accumulation in the adjacent left hemithorax. After splenectomy each patient became afebrile and repeated blood cultures were negative. The spleens of all three contained "infected" infarcts, and streptococci were cultured from two. Two of the patients are living at the present time, eight years and two and one-half years, respectively, following splenectomy and are free of evidence of infection. The third patient showed clinical improvement for about five years but later succumbed to congestive heart failure with evidence of severe rheumatic valvular disease.

SUMMARY

Splenectomy is a valuable therapeutic procedure in selected cases of subacute bacterial endocarditis in which adequate and appropriate antibiotic therapy fails. Three patients, whose case histories are presented, experienced complete remissions of the disease following splenectomy. In each case, an infected infarct of the spleen had apparently been the source of the persistent bacteremia.

X-ray films were made available by Dr. John A. Campbell, Department of Radiology, Indiana University Medical Center. Illustrations were prepared by Messrs. Paris Johnson and James F. Glore, Department of Illustration, Indiana University Medical Center.

REFERENCES

1. Keefer, C. S.: Present Day Treatment of Subacute Bacterial Endocarditis: The Minot Lecture, J. A. M. A. **152**:1397-1400 (Aug. 8) 1953.

2. Riesman, D.: Chronic Septicemic Endocarditis: With Splenomegaly Treatment by Splenectomy, J. A. M. A. **71**:10-12 (July 6) 1918.

3. Polowe, D.: Splenectomy in Treatment of Proved Subacute Bacterial Endocarditis: Report of a Case and Review of the Literature, Arch. Surg. **38**:139-147 (Jan.) 1939.

4. Fellinger, K., and Weissel, W.: Die Stellung der Milzexstirpation im Behandlungsplan der subakuten bakteriellen Endokarditis, Deutsche med. Wchnschr. **77**:499-502 (April 18) 1952.

5. Giraud, G.; Cazal, P.; Žatour, H.; Levy, A., and Puech, P.: Indications de la splenectomie dans la maladie d'Osler, Arch. mal. cœur. **47**:410-416 (May) 1954.

6. Lockwood, J. R.: Bacterial Endocarditis Associated with Spontaneous Rupture of the Spleen, New York J. Med. **51**:1188-1190 (May) 1951.

The Biophysics of the Variants of Sickle-Cell Disease

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Previous studies have demonstrated that the unique behavior of hemoglobin S with respect to polymerization, molecular orientation,[1] and decreased solubility consequent upon deoxygenation * is responsible for the sickling phenomenon and that blood from patients with sickle-cell disease shows increased number of sickled cells, increased erythrocyte mechanical fragility, and increased whole blood viscosity at reduced oxygen tensions.[4] The erythrocytes of sickle-cell anemia contain hemoglobin S in sufficient concentration to allow these changes to occur within the physiologic range of oxygen tensions; the erythrocytes of sickle-cell trait contain a concentration of hemoglobin S insufficient to show these changes except upon extreme reduction of the oxygen tension, to levels usually considered nonphysiologic. The relationship of these effects of dexoygenation to the mechanism of production of the hematologic abnormalities and circulatory alterations clinically seen in patients with sickle-cell disease has been discussed by Harris and his associates.[4]

The identification and description of patients in whom hemoglobin S occurs in association with another abnormal hemoglobin or in whom hemoglobin S coexists with another abnormal hematologic trait provided the opportunity for comparing the biophysical effects following deoxygenation in these conditions with the results obtained in sickle-cell anemia and sickle-cell trait and for evaluating the effects in the light of clinical severity of the various disease processes and in relation to the intracellular concentration of hemoglobin S.

These variants of sickle-cell disease are believed to represent examples of double heterozygosity [5]—the heterozygous hemoglobin S state in combination with the heterozygous state of the other abnormal hemoglobin or disease trait. At the time of this writing, hemoglobin S has been reported in association with (1) hemoglobin A (sickle-cell trait), (2) hemoglobin S with or without abnormal amounts of hemoglobin F (sickle-cell anemia), (3) hemoglobin C (sickle-cell-hemoglobin-C disease), and (4) hemoglobin D (sickle-cell-hemoglobin-D disease). Thalassemia,[6] ovalocytosis,[7] and hereditary spherocytic anemia [8] have also been reported in association with hemoglobin S. The studies reported here are mainly concerned with the biophysical changes (tactoid and gel formation, erythrocyte sickling and mechanical fragility, and whole blood viscosity alterations) produced by lowered oxygen tensions induced in blood obtained from patients with sickle-cell-hemoglobin-C disease and sickle-cell-thalassemia disease and com-

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Western Reserve University School of Medicine and the Department of Medicine, City Hospital. Scholar in Medical Science, John and Mary R. Markle Foundation (Dr. Harris).

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* References 2 and 3.

parison of these changes with similar observations on blood from patients with sickle-cell anemia and sickle-cell trait. In addition, data are presented on one patient with 30% fetal hemoglobin and 70% hemoglobin S, in whom a definite diagnosis has not been established.

METHODS

The methods used in this study have been described previously.[4] Hemoglobin solutions for the studies of tactoid formation and gelling were made by repeated freezing and thawing of thrice-washed red cells obtained from defibrinated blood. The total hemoglobin concentrations of these solutions ranged from 25 to 32 gm. per 100 ml. The formation of hemoglobin tactoids and sickled cells was induced by deoxygenation to the indicated oxygen tensions by equilibrating the hemoglobin solutions or cells with known gas mixtures. These gas mixtures contained varying amounts of oxygen and nitrogen but constant 10% CO_2 in order to limit alterations in pCO_2 and pH. The pH of the equilibrated blood samples ranged from 7.4 to 7.6, measured with a Beckman pH meter, model G. Hemoglobin analysis was performed by the method of paper electrophoresis slightly modified from that described by Smith and Conley,[9] with a barbital buffer of pH 8.6. Fetal hemoglobin determinations were estimated by the alkaline denaturation method of Singer.[10]

RESULTS

Hematologic Data on Patients in Study

Identifying data, representative blood cell counts, and cell indices for all patients in the present study are shown in the Table. The patients with sickle-cell trait, sickle-cell anemia, and sickle-cell-hemoglobin-C disease were all identified by the characteristic paper electrophoretic patterns of their hemoglobins. When examined prior to transfusions, the hemoglobins of the three patients with sickle-cell-thalassemia disease all showed on paper electrophoresis a characteristic pattern,[11] with the majority of the hemoglobin in the position of the hemoglobin S. A family study demonstrating the hereditary background of sickle-cell trait and thalassemia trait for Case 7 has been reported by Reich and Rosenberg.[12] Family studies in Case 9 are in progress †; they reveal a similar genetic background. Patient 10 was a 53-year-old Negro woman admitted to the hospital in the terminal azotemic stages of renal disease. She was anemic and had a positive sickle test. History did not reveal any previous symptoms attributable to anemia or sickle-cell disease. Fetal hemoglobin was calculated to be 30% of the total, and paper electrophoresis of her hemoglobin revealed only fetal and sickle hemoglobin; it has not been possible to identify any component of hemoglobin A. A 51-year-old sister, who was in good health, was not anemic (hemoglobin, 13.5 gm/100 ml). Fetal hemoglobin was also present as 30% of the total; the paper electrophoretic pattern of her hemoglobin was identical with that of Patient 10, and the sickle test was positive.

† Levine, B.: Personal communication to the authors.

Hematologic Values of Patients in Study

Case	Hemoglobin Electrophoretic Pattern	Fetal Hemoglobin, %	Red Blood Cells, Million/Cu. Mm.	Hemoglobin, Gm./100 Ml.	Hematocrit Value, %	Mean Corpuscular Volume, Cu. μ	Mean Corpuscular Hemoglobin, μγ	Mean Corpuscular Hemoglobin Concentration, Gm./100 Ml.	Reticulocytes, %	Icterus Index, Units
1	S-C	...	4.14	10.8	31	75	26	35	2.1	5
2	S-C	...	4.53	12.8	36.2	80	28	35	2.9	5
3	S-C	2.0	3.25	11.8	34.0	104	36	35	4.3	10
4	S-C	...	3.57	12.0	41.0	115	34	29	0.6	9
5	S-C	1.5	3.42	11.8	33	97	35	36	0.1	5
6	S-C	...	5.07	11.7	33.4	66	23	35	3.2	5
7	S. Thal.	2.5	5.2	10.6	33.8	65	20	31	3.4	9
8	S. Thal.	0.9	3.69	9.5	29.8	83	26	32	2.4	5
9	S. Thal.	14.3	4.41	9.8	30.0	68	22	33	1.6	7.5
10	S-F	30.0	3.67	7.4	23	63	20	32	4.0	5

Effect of Deoxygenation on the Formation of Tactoids and Gelling in Hemoglobin Solutions

Hemoglobin tactoids [1] and gel formation ‡ were produced in all disease variants of hemoglobin S that were studied by deoxygenation of the hemoglobin solutions at concentrations comparable to those found intracellularly. The results are presented in Figure 7. Upon step-wise reduction of the oxygen tension of a hemoglobin sample the solution, to the unaided eye, first becomes slightly opaque to transmitted light and flow within the equilibrating flask becomes noticeably slower. These minor alterations are associated with the appearance of small tactoids (1μ to 2μ in length), seen best with the phase microscope in dark-contrast. Upon further reduction of the oxygen tension the solutions become more opaque and the flow becomes slower, until gel formation finally occurs. During this process the microscopic tactoids steadily increase in size. No difference in this process or the end-result could be noted between the various hemoglobin combinations. However, the range of oxygen tensions at which the changes occurred was consistently different from one disease variant to the next. Hemoglobin solutions prepared from the erythrocytes of patients with sickle-cell anemia developed small tactoids at substantially higher oxygen tensions than those required to produce tactoids in the hemoglobin solutions prepared from the erythrocytes of patients with sickle-cell trait. Intermediate oxygen tensions initiated the production of tactoids in the hemoglobin combinations found in the patients with sickle-cell-hemoglobin-C and sickle-cell-thalassemia disease. The phenomenon of gelation occurred in the same relative order, although at somewhat lower oxygen tensions for each hemoglobin combination. In the total hemoglobin range of 25 to 32 gm/100 ml. the concentration had no appreciable effect upon the appearance of tactoids or gelation relative to a given oxygen tension.

‡ References 1 and 13.

Effect of Deoxygenation on the Number of Sickled Cells and Whole Blood Viscosity

Figures 1, 2, 3, and 4 show the effects of deoxygenation on the number of sickled cells and on the viscosity of whole blood from patients with sickle-cell-hemoglobin-C and sickle-cell-thalassemia diseases. The shaded areas in these figures represent the range of results that have been obtained from patients with sickle-cell anemia and sickle-cell trait. To define these ranges data from this and the previous study [4] have been combined and comprise the experience to date on a total of six patients with sickle-cell trait and nine patients with sickle-cell anemia. In Figures 1 and 3 the number of sickled cells is recorded as the percent sickled of the total number of cells. Because of anemia one patient with sickle-cell-thalassemia disease (Case 7) required transfusions shortly before study, and, consequently, this one curve is plotted as per cent of the maximum number of sickled cells.

Because of variations in the maximum absolute viscosity from patient to patient, the viscosity changes are plotted in Figures 2 and 4 as per cent of the maximum increase obtained at complete deoxygenation. Although, as would be expected, after transfusion in the patient referred to above the changes in absolute viscosity were less than those seen in the other patients, the percentage increases relative to the maximally achieved value upon deoxygenation are very similar.

It is apparent from the data that for those diseases associated with hemoglobin S progressive reduction in oxygen tension (and, consequently, hemoglobin saturation) is accompanied by progressive increases in the number of sickled forms. However, the range of oxygen tensions at which the changes were induced differed according to the disease variant.

Comparison of Figures 1 and 3 with Figures 2 and 4 demonstrates the similarity in the types of response for whole blood viscosity and number of sickled cells and, furthermore, indicates the close correlation between sickling and viscosity.

EFFECT OF DEOXYGENATION ON THE PER CENT SICKLED CELLS IN SICKLE-C DISEASE

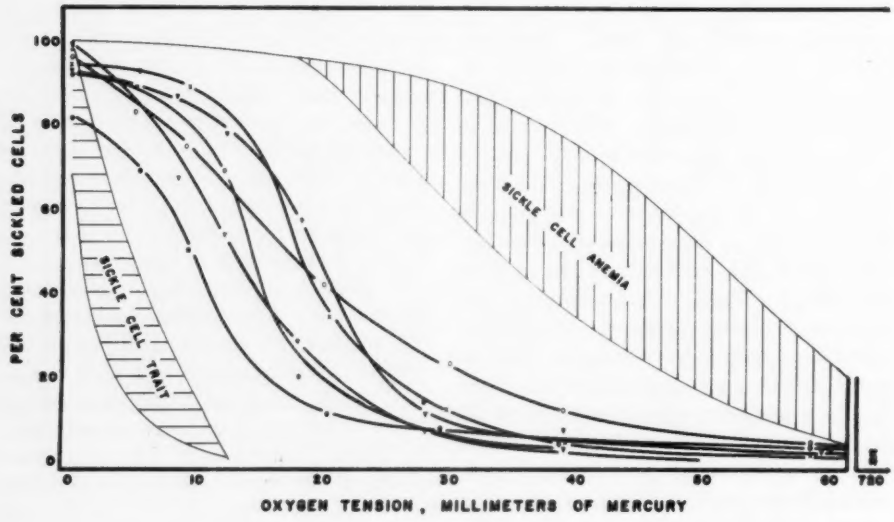

Figure 1

EFFECT OF DEOXYGENATION ON THE VISCOSITY OF WHOLE BLOOD IN SICKLE-C DISEASE

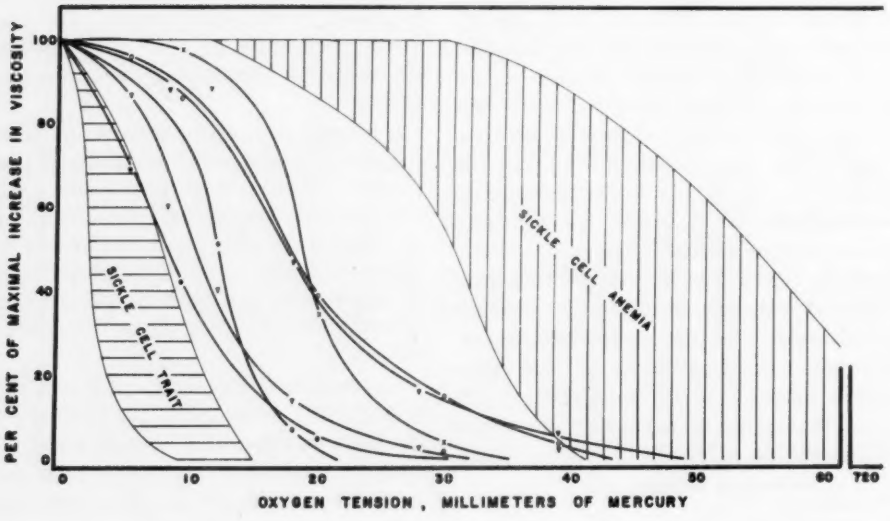

Figure 2

EFFECT OF DEOXYGENATION ON THE PER CENT SICKLED CELLS
IN SICKLE-THALASSEMIA DISEASE

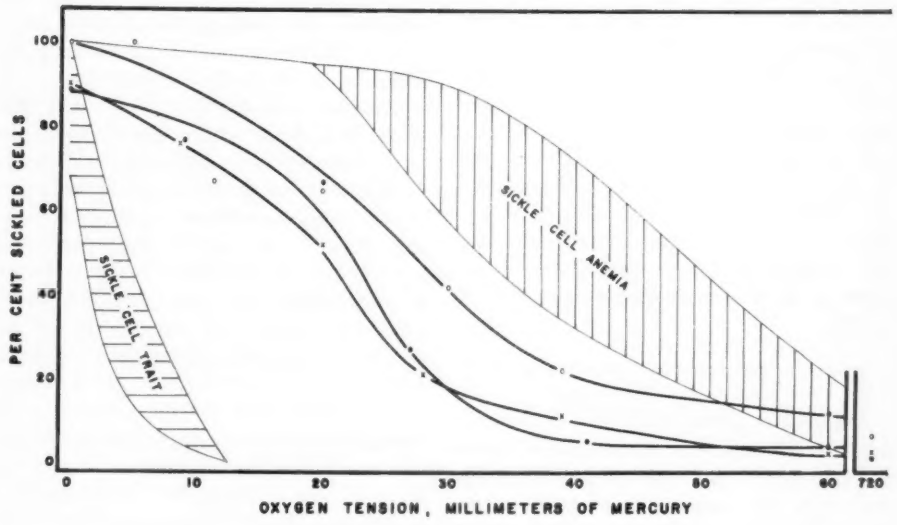

Figure 3

EFFECT OF DEOXYGENATION ON THE VISCOSITY OF WHOLE BLOOD
IN SICKLE-THALASSEMIA DISEASE

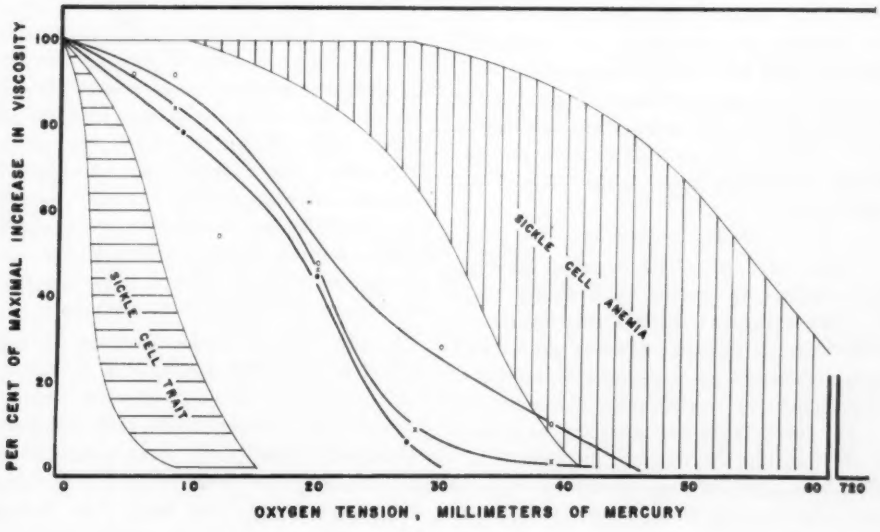

Figure 4

Artificial mixtures of sickle cells with normal cells—inert with respect to sickling and viscosity changes—show upon complete deoxygenation a straight-line relationship between the number of sickle cells present in the mixture and the absolute viscosity. By the methods used here the absolute viscosity of normal blood or of blood from patients with sickle-cell disease in the oxygenated form ranged from four to six times that of water. With complete deoxygenation the maximum absolute viscosities produced ranged from 9 to 16 times that of water and are comparable to the viscosity of polycythemic blood at a hematocrit value of 70% to 80%.

Effect of Deoxygenation on Erythrocyte Mechanical Fragility

The results of the studies on erythrocyte mechanical fragility are presented in Figure 5. From the data from this and the previous study [4] it was observed that at an oxygen tension of 720 mm. Hg the mechanical fragility of blood from patients with sickle-cell anemia was slightly above normal. Blood from patients with sickle-cell anemia and sickle-cell-hemoglobin-C and sickle-cell-thalassemia diseases all showed significant elevations of mechanical fragility at oxygen tensions at 50 mm. Hg and below. In contrast, blood from patients with sickle-cell trait did not exhibit any alteration in mechanical fragility until the oxygen tension had been reduced to 10 mm. Hg. At an oxygen tension of 0 mm. Hg the mechanical fragilities ranged from 37% to 61% and there were no consistent differences between the various disease states.

Studies in Case 10

Studies of whole blood viscosity, sickling, and erythrocyte mechanical fragility were carried out on blood samples from Patient 10. The data for viscosity changes at reduced oxygen tensions are presented in Figure 6. The number of sickled cells increased in a similar curve, beginning at an oxygen tension of 30 mm. Hg. Erythrocyte mechanical fragility was not elevated above the normal until the oxygen tension was reduced to 30 mm. Hg or lower.

Comment

The interpretation and significance of the effects of deoxygenation upon extracellular and intracellular hemoglobin S (tactoid, gel formation, and sickling) and upon the intercellular relations (viscosity) as effecting the dynamics of blood flow and production of hematologic abnormalities have been discussed in some detail previously.[4] From the data presented here and those outlined in Figure 7, a general correlation can be drawn between the intracellular concentration of hemoglobin S, the oxygen tension at which tactoids and gel formation occur in hemoglobin solutions, the oxygen tension at which intact cells sickle, and the severity of the anemia and symptoms associated with sickle-cell disease. The in vivo and in vitro effects of deoxygenation upon the red cell containing hemoglobin S seem to be directly related to the intracellular concentration of the hemoglobin S. For a hemoglobin S concentration of 90% to 100%, as observed in the erythrocytes of clinically severe sickle-cell anemia, an oxygen tension as high as 60 mm. of mercury produces in vitro the biophysical changes of increased numbers of sickled cells, increased mechanical fragility, and increased whole blood viscosity. For hemoglobin S concentrations of 50% to 80%, as observed in clinically intermediate sickle-cell-hemoglobin-C and sickle-cell thalassemia diseases, a lower oxygen tension, 40 mm. of mercury, is required to produce comparable biophysical changes. Both of these oxygen tensions are known to be within the physiologic range. However, to produce the same biophysical changes for hemoglobin S concentrations of 24% to 45%, as observed in the clinically benign, nonanemic sickle-cell trait, the oxygen tension must be reduced below the usual physiologic level, to 10 mm. of mercury.

In addition, the studies in Case 10, with 30% fetal and 70% hemoglobin S, support the correlation between oxygen tension, hemoglobin S concentration, and symptoms. Biophysical alterations were produced in blood samples from the patient only when the oxygen tension was reduced to 30 mm. Hg. Sickling changes occurred only at a

EFFECT OF DEOXYGENATION ON ERYTHROCYTE MECHANICAL FRAGILITY
IN THE VARIANTS OF SICKLE CELL DISEASE

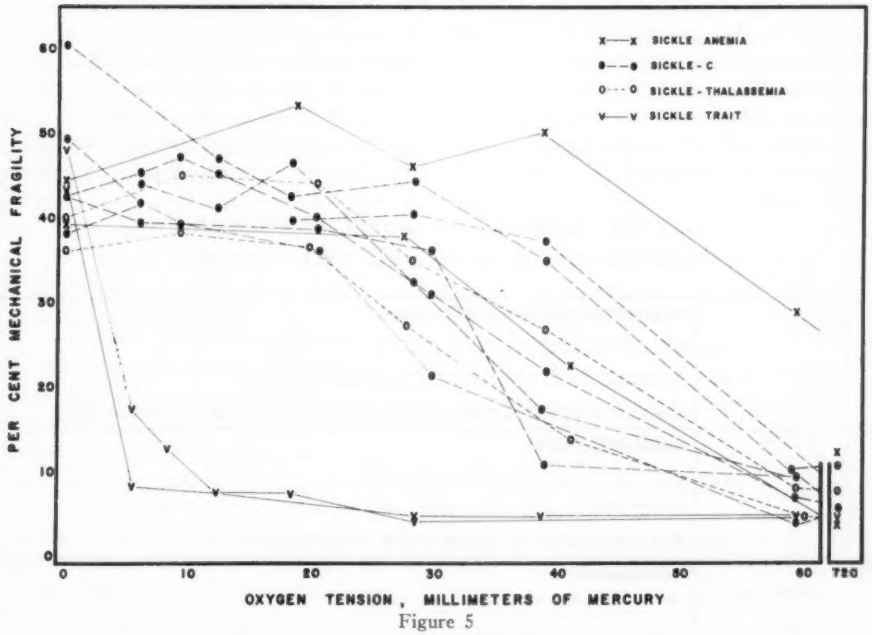

Figure 5

EFFECT OF DEOXYGENATION ON THE VISCOSITY OF WHOLE BLOOD

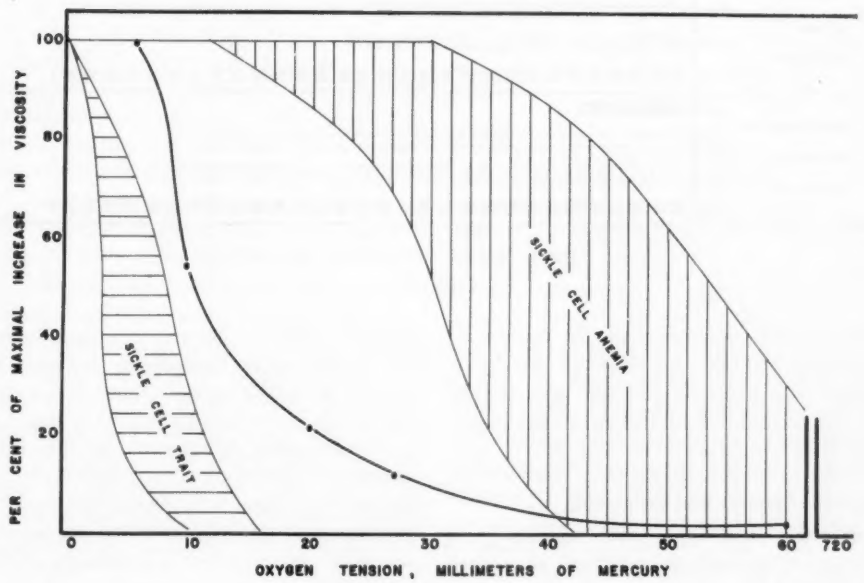

Figure 6 (Case 10)

tension lower than would be expected for the 70% hemoglobin S found on analysis. However, it has been shown by Singer and co-workers [13] that hemoglobin F does not enter into tactoid and gel formation as does hemoglobin A and therefore the amount of hemoglobin which can contribute to the red cell sickling is in effect significantly lower than would be indicated by hemoglobin analysis. This patient had no history of symptoms referable to sickle-cell disease or anemia and probably had not been anemic prior to her terminal illness, a supposition supported by studies on her sister, who showed a similar hemoglobin composition, negative history, and no anemia.

It was found that small tactoids were formed in hemoglobin solutions at oxygen tensions higher than those required to produce detectable increases in the number of sickled cells (Fig. 7). A comparison of Figure 5 with Figures 1 and 2 shows that the erythrocyte mechanical fragility in sickle-cell-hemoglobin-C and sickle-cell-thalassemia diseases is significantly elevated at oxygen tensions higher than are required to produce the first increase in number of intact sickled cells. These observations suggest that deoxygenation initiates in the red cells some alteration which is not immediately reflected in a gross detectable shape change but which does result in increased mechanical fragility. Conceivably, this change could be due to the intracellular formation of small tactoids which are not large enough to distort the external appearance of the cell but which are accompanied by an increased susceptibility of the cell to disruption by mechanical trauma.

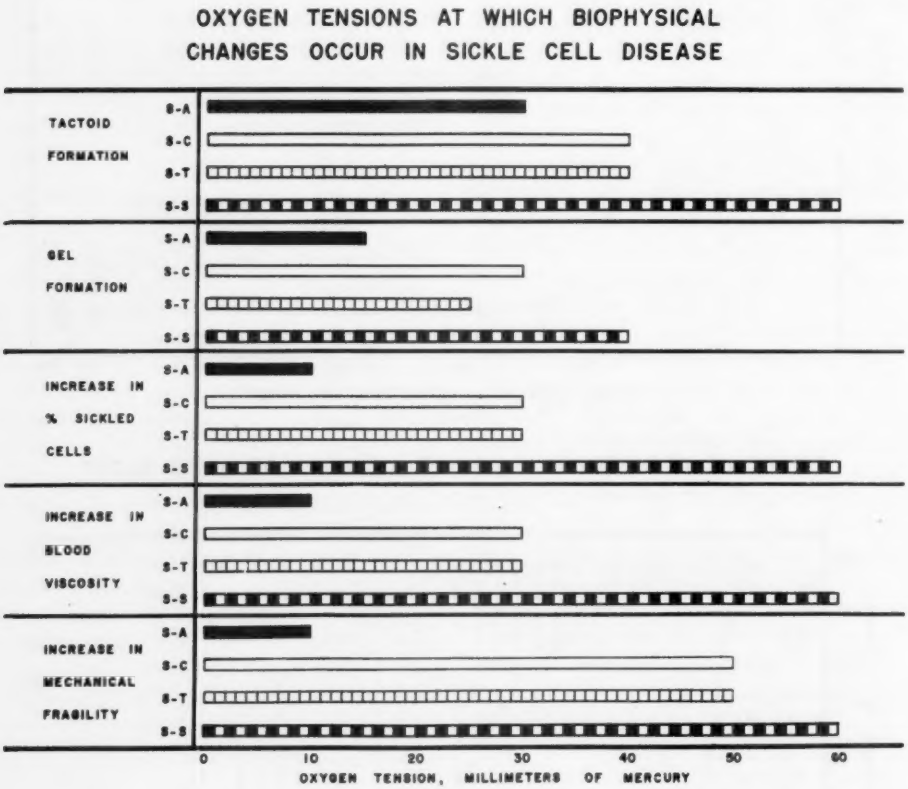

Figure 7

Sydenstricker, in 1924,[14] was apparently the first to propose that the increased rate of cell destruction seen in sickle-cell anemia was due to the sickling abnormality of the erythrocyte. He also believed that the hemolysis was brought about by a "hereditary defect of the spleen." In 1927, Hahn and Gillespie [15] discounted the role played by the spleen and clearly stated that "reasons exist for believing that the only specific cause for active sickle cell anemia is in the unique hereditary anomaly of the red corpuscles which predisposes to it." At present the final critical evidence is not yet available to provide a definitive answer to this question: Does the sickling phenomenon play a causative role in the decreased life span of the sickle cell? It has been argued that the augmented rate of cell destruction would proceed irrespective of the sickling change. In support of this it is pointed out that there is increased erythrocyte destruction in various of the other hemoglobinopathies when not associated with the sickle anomaly (i. e., homozygous hemoglobin C). However, since the mode of red cell destruction in these hemolytic disorders is obscure, it would seem that this analogy is as impossible to maintain as to refute.

Observations that have been taken as evidence against the sickling process being causally related to erythrocyte destruction are those of Reinhard and co-workers § and Tinsley and associates,[18] who have reported that the administration of high oxygen tensions in the inspired air to patients with sickle-cell anemia decreased the number of sickled cells in the peripheral blood but did not detectably decrease the rate of cell destruction. In these studies the venous saturation was increased to a maximum of 63% by the administration of oxygen. On the basis of the studies presented here, this maximum oxygen saturation would still be within the range where continuing biophysical alterations of the red cell would be expected, and, consequently, little or no decrease in the rate of hemolysis would be anticipated. Callender and co-workers [19] studied the survival of sickle-cell anemia erythrocytes transfused into normal recipients breathing high concentrations of oxygen. Equivocal results were obtained. However, in one recipient the rate of red cell destruction increased [19] when the oxygen was discontinued. These workers also transfused cells from a patient with sickle-cell trait into a chronically cyanotic recipient. These cells appeared to survive a normal length of time. Again on the basis of the finding reported here, the reduction in oxygen tension in the recipient was undoubtedly not sufficient to produce any alteration in sickle trait cells.

The administration of dimercaprol U. S. P. (BAL; 2,3-dimercaptopropanol) has been reported to cause increased intravascular sickling without the development of symptoms.‖ Kuhns [20] administered dimercaprol to a patient with presumed sickle-cell trait, and this did not cause an increase in intravascular sickling, although the in vitro susceptibility of the cells to sickling was increased. Sufficient data to evaluate these observations are not available.

Studies during World War II showed no evidence of rejection or disability from sickle-cell trait among Negro flying personnel. Henderson and Thornell [21] studied one subject with sickle-cell anemia and four with sickle-cell trait under simulated flight conditions in a low-pressure chamber for a period of two hours. They found no increase in sickling in sickle trait, but in the subject with sickle-cell anemia the number of sickled cells increased from 8% in the control period to 15% at a simulated altitude of 16,000 feet. At that altitude the arterial oxygen saturation was 74%. This oxygen saturation is comparable to the in vitro studies presented here at an oxygen tension of 50 to 60 mm. of mercury, at which tension a sickle-cell count of 15% falls within the range obtained by us for sickle-cell anemia. In their short-term experiment Henderson and Thornell found no evidence of a change in red cell destruction or production as determined by changes

§ References 16 and 17.

‖ Thomas, L., and Stetson, C. A., Jr., cited by Smith.[23]

in reticulocytes, icteric index, or urine urobilinogen. No adverse effects were noted.

On the other hand, the hazards of reduced oxygen tensions to persons with sickle-cell disease are becoming more and more apparent in the recent reports of the development of splenic infarction during airplane flight. This complication has occurred in persons with sickle-cell anemia, in those with sickle-hemoglobin-C disease, and in persons with well documented sickle-cell trait.¶

The pathogensis of the splenic infarcts is best explained in the light of present knowledge on the basis of vascular occlusive phenomenon secondary to the formation of sickle-cell thrombi. Studies by Dreyer and Budtz-Olsen [25] have demonstrated that the half-dozen or so main branches of the splenic artery do not intercommunicate to any great extent. This may account for the predisposition of the spleen to infarction in contrast to other organs presumably under a somewhat similar stress of lowered oxygen tension. Also, Weisman and co-workers [26] have shown that transfused sickle cells are trapped and concentrated within the normal splenic pulp. Therefore, even a slight increase in circulating sickled cells could result in the accumulation of a larger number of sickle cells within the spleen. Peripheral blood studies would then not reflect the concentration of sickled cells within the spleen. Jandl and co-workers [27] have demonstrated in one case concentration of sickled cells within the liver. However, infarction of the liver would be more unlikely because of its peculiar circulation.

During airplane flight it is suggested that the following course of events takes place. The moderate reduction of oxygen tension of inspired air leads to a decrease in blood oxygen tension sufficient to initiate sickling. The sickled cells are concentrated within the splenic pulp. This leads to increased viscosity and slowing of the blood flow, further reduction in oxygen tension, accumulation of CO_2, and lowering of the pH. This in turn would lead to further sickling, and the continuation of this self-perpetuating cycle would eventually result in complete obstruction of blood flow and tissue infarction. This explanation seems quite satisfactory for patients with sickle-cell anemia and sickle-cell-hemoglobin-C disease. However, at present, no critical studies are available to demonstrate that the extreme reduction in oxygen tension necessary to initiate this course of events in sickle-cell trait can occur. However, the probable role of oxygen tension is supported by the observation of Smith and Conley [23] that at relatively low altitudes (6000 feet) splenic infarction occurred in two patients with the more susceptible sickle-cell-hemoglobin-C disease, while the splenic infarctions in persons with sickle-cell trait had occurred after flights at higher altitudes.

The severity of the anemia seen in any patient with sickle-cell disease is, of course, dependent upon the balance established between erythrocyte destruction and production. Because of this balance, only incompletely evaluated at present, it seems evident that measurements concerning factors contributing to the rate of erythrocyte destruction could have only a general correlation with the degree of anemia and that individual case exceptions are to be expected because of variations in rate of production. In addition, factors other than the concentration of hemoglobin S have been shown to affect the sickling process: pH, bile salts, soaps, total hemoglobin concentrations, interaction between various types of hemoglobin, and alterations in sulfhydryl metabolism.# It has been possible to demonstrate that potassium is involved in the sickling phenomenon.*

The observations presented here further extend the previously reported observations [4] and lend additional support to the hypothesis that the in vitro behavior of hemoglobin S and sickle cells at reduced oxygen tensions correlates with the severity of the clinical and hematological manifestations seen in the patient.

¶ References 22-24.

References 13, 28, and 29 and Kass, E. H., and others: Unpublished data.

* Griggs, R. C., and Harris, J. W.: Unpublished data.

CONCLUSIONS

The data presented here support the theory that (1) the sickling phenomenon plays a critical role in the pathogenesis of many of the symptoms seen in sickle-cell disease and in the shortened life span of sickle cells; (2) the severity of both the circulatory alterations and anemia is related to the response of the sickle cell to changes in oxygen tension; (3) this response is mainly dependent upon the intracellular concentration of sickle hemoglobin.

Dr. Benett Levine, Mt. Sinai Hospital, Cleveland, gave permission to study Cases 7 and 9. Miss Virginia Grant and Mrs. Phyllis Fersky gave technical assistance.

REFERENCES

1. Harris, J. W.: Studies on the Destruction of Red Blood Cells: VIII. Molecular Orientation in Sickle Cell Hemoglobin Solutions, Proc. Soc. Exper. Biol. & Med. **75**:197, 1950.

2. Perutz, M. F., and Mitchison, J. M.: State of Haemoglobin in Sickle-Cell anaemia, Nature, London **166**:677, 1950.

3. Perutz, M. F.; Liquori, A. M., and Eirich, F.: X-Ray and Solubility Studies of the Haemoglobin of Sickle-Cell Anaemia Patients, Nature, London **167**:929, 1951.

4. Harris, J. W.; Brewster, H. H.; Ham, T. H., and Castle, W. B.: Studies on the Destruction of Red Blood Cells: X. The Biophysics and Biology of Sickle-Cell Disease, A. M. A. Arch. Int. Med. **97**:145, 1956.

5. Neel, J. V.: Implications of Some Recent Developments in Hematological and Serological Genetics, Am. J. Human Genet. **6**:208, 1954.

6. Silvestroni, E., and Bianco, I.: Microdrepanocito-anemia in un soggetto di razza bianca, Boll. atti Accad. med. Roma **70**:347, 1944-1945.

7. Fadem, R. S.: Ovalocytosis Associated with the Sickle-Cell Trait, Blood **4**:505, 1949.

8. Smith, E. W., and Conley, C. L.: Clinical Features of the Genetic Variants of Sickle Cell Disease, Bull. Johns Hopkins Hosp. **94**:289, 1954.

9. Smith, E. W., and Conley, C. L.: Filter Paper Electrophoresis of Human Hemoglobin with Special Reference to the Incidence and Clinical Significance of Hemoglobin C, Bull. Johns Hopkins Hosp. **93**:94, 1953.

10. Singer, K.; Chernoff, A. I., and Singer, L.: Studies on Abnormal Hemoglobins: I. Their Demonstration in Sickle Cell Anemia and Other Hematologic Disorders by Means of Alkali Denaturation, Blood **6**:413, 1951.

11. Singer, K.; Singer, L., and Goldberg, S. R.: Studies on Abnormal Hemoglobins: XI. Sickle Cell-Thalassemia Disease in the Negro; The Significance of the S+A+F and S+A Patterns Obtained by Hemoglobin Analysis, Blood **10**:405, 1955.

12. Reich, R. S., and Rosenberg, N. J.: Aseptic Necrosis of Bone in Caucasians with Chronic Hemolytic Anemia Due to Combined Sickling and Thalassemia Traits, J. Bone & Joint Surg. **35-A**: 894, 1953.

13. Singer, K., and Singer, L.: Studies on Abnormal Hemoglobins: VIII. The Gelling Phenomenon of Sickle Cell Hemoglobin; Its Biologic and Diagnostic Significance, Blood **8**:1008, 1953.

14. Sydenstricker, V. P.: Further Observations on Sickle Cell Anemia, J. A. M. A. **83**:12, 1924.

15. Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia: Report of a Case Greatly Improved by Splenectomy, Arch. Int. Med. **39**:233, 1927.

16. Reinhard, E. H.; Moore, C. V.; Dubach, R., and Wade, L. J.: The Effect of Breathing 80 to 100% O_2 on Erythrocyte Equilibrium in Patients with Sickle Cell Anemia, J. A. M. A. **121**: 1245, 1943.

17. Reinhard, E. H.; Moore, C. V.; Dubach, R., and Wade, L. J.: Depressant Effects of High Concentrations of Inspired Oxygen on Erythrocytogenesis: Observations on Patients with Sickle Cell Anemia with a Description of the Observed Toxic Manifestations of Oxygen, J. Clin. Invest. **23**:682, 1944.

18. Tinsley, J. C., Jr.; Moore, C. V.; Dubach, R.; Minnich, V., and Grinstein, M.: The Role of Oxygen in the Regulation of Erythropoiesis: Depression of the Rate of Delivery of New Red Cells to the Blood by High Concentrations of Inspired Oxygen, J. Clin. Invest. **28**:1544, 1949.

19. Callender, S. T. E.; Nickel, J. F.; Moore, C. V., and Powell, E. O.: Sickle Cell Disease: Studied by Measuring the Survival of Transfused Red Blood Cells, J. Lab. & Clin. Med. **34**:90, 1949.

20. Kuhns, W. J.: Effects of the Intramuscular Administration of BAL (2,3-dimercaptopropanol) in a Subject with the Sickle Cell Trait: Case Report, Blood **4**:1240, 1949.

21. Henderson, A. B., and Thornell, H. E.: Observations on the Effect of Lowered Oxygen Tension on Sicklemia and Sickle Cell Anemia Among Military Flying Personnel, J. Lab. & Clin. Med. **31**:769, 1946.

22. Conn, H. O.: Sickle-Cell Trait and Splenic Infarction Associated with High-Altitude Flying, New England J. Med. **251**:417, 1954.

23. Smith, E. W., and Conley, C. L.: Sicklemia and Infarction of Spleen During Aerial Flight: Electrophoresis of the Hemoglobin in 15 Cases, Bull. Johns Hopkins Hosp. **96**:35, 1955.

24. Motulsky, A. G.; Luttgens, W. F.; Paterson, W., and Rotter, R.: Splenic Infarction Precipitated by Airplane Flight in Patients with Sicklemia, Clin. Res. Proc. **3**:51, 1955.

25. Dreyer, B., and Budtz-Olsen, O. E.: Splenic Venography: Demonstration of the Portal Circulation with Diodone, Lancet **1**:530, 1952.

26. Weisman, R., Jr.; Ham, T. H.; Hinz, C. F., and Harris, J. W.: Studies of the Role of the Spleen in Destruction of Erythrocytes, Tr. A. Am. Physicians **68**:131, 1955.

27. Jandl, J. H.; Greenberg, M. S.; Yonemoto, R. H., and Castle, W. B.: Clinical Determination of the Sites of Red Cell Destruction, Clin. Res. Proc. **3**:95, 1955.

28. Sydenstricker, V. P.; Mulherin, W. A., and Hanseel, R. W.: Sickle Cell Anemia: Report of Two Cases in Children, with Necropsy in One Case, Am. J. Dis. Child. **26**:132, 1932.

29. Rebuck, J. W.; Monto, R. W., and Sturrock, R. M.: The Structural Basis of Sickling and Its Electron Microscopy, Am. J. Path. **28**:530, 1952.

Pulmonary Stenosis with Increased Pulmonary Blood Flow

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For a number of years prior to the advent of widespread use of cardiac catheterization, the syndromes associated with pulmonary stenosis and right-to-left shunts through atrial and ventricular septal defects had been well described. In the past few years cardiac catheterization performed on a large number of patients has allowed recognition of the syndrome of pulmonary stenosis with left-to-right shunt. As expected from knowledge of the relative frequency of the various types of left-to-right shunts, the pulmonary stenosis is usually associated with atrial or ventricular septal defects or, less commonly, patent ductus arteriosus, anomalous pulmonary venous connection, or other rarer causes of left-to-right shunt.

Abrahams and Wood [1] called attention to this syndrome in 1951 under the designation of pulmonary stenosis with normal aortic root. Since that time, one or two papers have appeared in the literature each year describing a small number of such cases. In 1952 Gøtzsche [2] described 3 cases among 201 catheterized subjects, Deuchar and Zak [3] observed 4 cases among 130 patients, and Broadbent and co-workers [4] reported on 10 cases. In 1954 Moffitt and co-workers [5] reported 6 cases; Magidson and associates,[6] 14 cases, and Rudolph and associates,[7] 10 cases. In 1955 Eldridge and Hultgren [8] reported 8 cases among 250 cardiac catheterizations and observed an additional 3 cases between the time of submission and the time of publication of their paper. We have performed heart catheterizations on nine such cases in the past one and one-half years and believe that the syndrome is probably much commoner than was previously realized.

A number of authors have reported only noncyanotic cases or have implied that the syndrome should be restricted to cases of left-to-right shunt; however, in most of the reports by these observers the protocols revealed that at least a few patients in each series gave a history of cyanosis, showed a drop in arterial oxygen saturation with exercise or showed significant arterial oxygen unsaturation at the time of cardiac catheterization. We feel that this exclusion is artificial, as the presence or absence of cyanosis in each case will depend upon the relative resistance-flow characteristics on the two sides of the circulation, anatomical or functional overriding of the aorta, directed flow, etc. We believe that the only criteria for inclusion in this group are the presence of a left-to-right shunt with pulmonary stenosis and increased pulmonary blood flow, or at least a pulmonary flow which is greater than systemic flow. Our cases are somewhat different from those previously reported in the literature in that they represent a younger age group, with a mean of 5.3 years, and in that there was a greater number of cases with cyanosis. This report presents six cases of ventricular septal defect with pulmonary

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TABLE 1.—*Clinical Findings in Nine Cases of Pulmonary Stenosis with Left-to-Right Shunt* *

Case No.	Age	Sex	Final Diagnosis	Symptoms and General Signs	Cardiac Enlargement by Phy. Exam.	Left Chest Bulge	Precordial Heave	Murmurs	Thrill	P_2	EKG	Fluoroscopy	Other Studies
1	8 yr.	M	Right-sided aortic arch, overriding aorta, infundibular pulmonic stenosis with R. to L. and L. to R. shunts	Slightly cyanotic since birth; S.O.B. with exertion; cyanosis of nails 1*; clubbing 2	2	2	2	S 2, 3d LICS; EDM 2, 2d LICS; to and fro over upper sternum	0	Inc. 1, single	RVH 2	RVH 3; boot-shaped with concavity of infundibulum & Rt. sided aortic arch; vessels Inc. 1 with pulsation 1	Dye curve showed small R. to L. & large L. to R. shunt
2	6 mo.	F	Ventricular septal defect, mild pulmonary valvular stenosis with large R. to L. and L. to R. shunts	Severe cyanosis since birth with respiratory distress and failure to gain weight; respiratory infections; generalized cyanosis with clubbing 1	1	1	1	S 2, 3d LICS	0	Inc. 1, single	Normal infantile	Generalized enlargement 1; hilar vessels Inc. 2 with pulsation 2; P A segment N	O_2 Sat. breathing air 60%, with marked respiratory variation in O_2 saturation
3	4 mo.	F	Ventricular septal defect with infundibular pulmonic stenosis; pulmonary hypertension and L. to R. shunt	Heart murmur since birth; prolonged respiratory infection with fever; never cyanotic	1	0	1	S 3, 2d & 3d LICS; EDM 2, 2d LICS	S 2, 2d LICS	Inc. 1, single	RVH 3	RVH 1; P A segment Inc. 1; vessels Inc. 1, with pulsation 1	.....
4	10 yr.	M	Ventricular septal defect with L. to R. shunt, mild infundibular and valvular stenosis; pulmonary hypertension	Slowly increasing S.O.B. with exertion since birth; mild cyanosis with exercise; frequent respiratory infections	1	1	1	S 3, 3d & 4th LICS	S 2, 3d & 4th LICS	Inc. 2, single	Complete RBBB; high P waves	General enlargement with prominent pulsatile pulmonary trunk; hilar vessels Inc. 2 with pulsation 2	Dye curve showed L. to R. shunt 3 with slight R. to L. shunt
5	5 yr.	F	Ventricular septal defect with mild pulmonary stenosis and moderate L. to R. shunt	Murmur since birth; asymptomatic	0	0	0	S 2, 2d & 3d LICS	0	N, split 2	RVH 1	Slight prominence of pulmonary trunk; hilar vessels N with pulsation 1	.....
6	6 yr.	M	Ventricular septal defect with infundibular pulmonic stenosis; moderate L. to R. shunt	Murmur since birth; slight dyspnea on exertion	0	0	0	S 2, 2d & 3d LICS	0	N	RVH 1	Slight concavity of pulmonary trunk; hilar vessels N with pulsation 1	.....
7	6 yr.	F	Valvular pulmonary stenosis with atrial septal defect and moderate L. to R. shunt	Normal birth history; exertional dyspnea and weakness; episodic cyanosis and syncope past 2 yr.; frequent respiratory infections	0	0	0	S 3, 2d LICS; EDM 1, 2d LICS	S 1, 2d LICS	Dec., single	RVH 2; Inc. P waves	RVH 1; prominent pulmonary trunk 3 with pulsation 2; hilar vessels Inc. 2 with pulsation 2	No drop in O_2 Sat. with exercise; dye-dilution curve showed L. to R. shunt 2
8	25 yr.	F	Atrial septal defect with infundibular pulmonic stenosis; moderate L. to R. and small R. to L. shunt	Exertional dyspnea 2; cyanosis with exercise; clubbing 1; cyanosis 1	2	1	3	S 2, 2d LICS; EDM 2, 2d LICS; AMDM 2	0	Inc. 1, single	RVH 3; Inc. P waves; A-V dissociation	RVH 2 with concavity of infundibulum; hilar vessels Dec. but with pulsation 1 to 2	O_2 Sat. at rest 88% with fall to 70% with exercise; Resp. variation in O_2 Sat.; dye curve showed small R. to L. and L. to R. shunt 2
9	8 yr.	M	Atrial septal defect, valvular pulmonic stenosis and L. to R. shunt	Exertional dyspnea 1	0	0	0	S 3, 2d LICS; EDM 1, 2d LICS	S 1, 2d LICS	N, single	RVH 1	RVH with Inc. pulmonary trunk 2; hilar vessels Inc. 1, with pulsation 1	No drop in O_2 Sat. with exercise; dye curve showed L. to R. shunt 2

* All grading is on the basis of 1 to 4. M, male; F, female; R. to L., right to left; L. to R., left to right; S.O.B., shortness of breath; S, systolic murmur or thrill (graded 1 to 4); LICS, left intercostal space; EDM, early diastolic murmur; AMDM, apical middiastolic murmur; Inc., increased; Dec., decreased; RVH, right ventricular hypertrophy; RBBB, right bundle branch block; P A, pulmonary artery; N, normal; Sat., saturation.

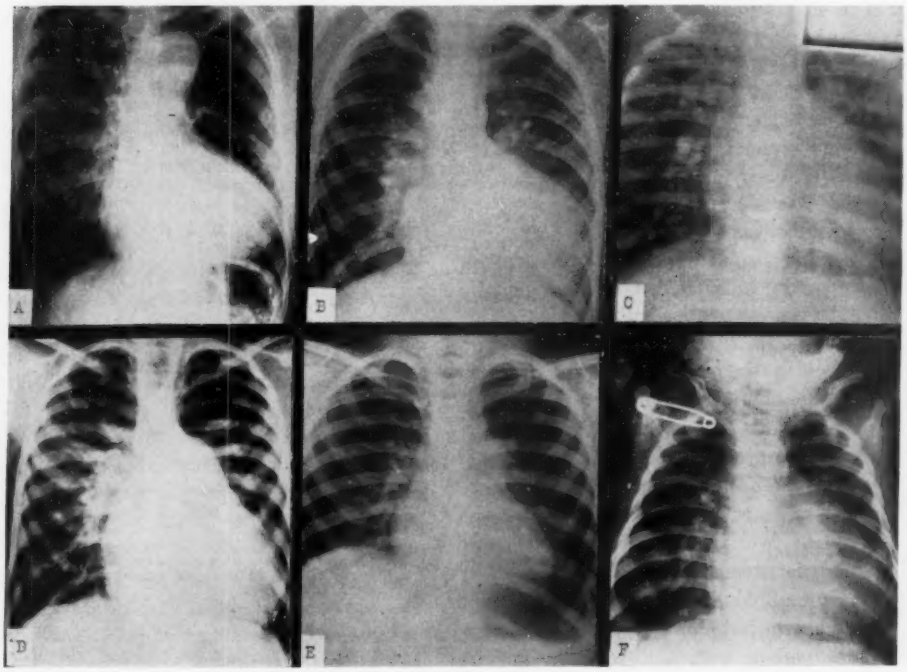
stenosis and three cases of atrial septal defect with pulmonary stenosis. All patients showed increased pulmonary blood flow and pulmonary flows greater than systemic flows.

CLINICAL FINDINGS

Table 1 summarizes the clinical data on these nine cases. The ages of the patients ranged from 4 months to 25 years, and all but one of the patients were 10 years or younger. The symptoms were extremely variable from patient to patient. One patient was asymptomatic; another was severely cyanotic and undernourished, had failed to grow properly, was dyspneic at rest, and had frequent respiratory infections. Between these extremes of symptoms, the remainder of the patients usually had mild to moderate dyspnea with exertion. Two of the group had been cyanotic since birth; one of the patients had developed progressive cyanosis over the past few years, and two gave a past history of exertional or episodic cyanosis. Four gave a history of frequent respiratory infections.

Physical examination revealed mild to moderate cardiac enlargement in five cases. Left thoracic bulge or precordial heave were present in five patients. A systolic murmur of Grade 2 to 3 intensity (on the basis of 4), maximal in the area about the second or third left intercostal spaces at the left sternal border, was present in all cases. In the cases of ventricular septal defect the murmur was maximal at the third left intercostal space or slightly below this area in all cases. It was associated with an additional systolic murmur and thrill in the pulmonary area in one and with a systolic thrill in the third

Fig. 1.—Some representative chest roentgenograms. *A* (Case 8), infundibular stenosis with atrial septal defect. The projection is slightly oblique, to show the character of the hilar vessels. Although the hilar vessels are small, they were observed fluoroscopically to pulsate prominently. *B* (Case 1), infundibular stenosis with membranous septal defect. The hilar vascular shadows were increased and pulsated prominently. *C* (Case 2), ventricular septal defect with valvular pulmonary stenosis. *D* (Case 4), ventricular septal defect with mild valvular and infundibular pulmonic stenosis. *E* (Case 7), valvular pulmonic stenosis with atrial septal defect. *F* (Case 3), ventricular septal defect with mild infundibular stenosis.



left intercostal space in another. In only one of the cases of ventricular septal defect and pulmonary stenosis was it possible to separate phonocardiographically a "diamond-shaped" systolic murmur in the plmonary area from a "plateau" systolic murmur lower to the left of the sternum, although in five cases the systolic murmur was heard well in the pulmonary area and transmitted well to the intraclavicular area. In all the cases of atrial septal defect with pulmonary stenosis the murmur was maximal in the second left intercostal space. In two of the cases the murmur was characteristic of pulmonic stenosis and associated with a thrill and decreased single pulmonary second sound. In the third patient the systolic murmur was considered characteristic of atrial septal defect, with somewhat increased, but single, pulmonary second sound. An early diastolic murmur maximal in the pulmonary area was present in two of the cases of ventricular septal defect and in all three of the cases of atrial septal defect. In addition, one of the cases of atrial septal defect showed an apical mid-diastolic murmur.

The electrocardiogram showed right ventricular hypertrophy of the "concentric" type (Grade I to III) in seven of the cases. In one case of ventricular septal defect and pulmonary stenosis the electrocardiogram showed complete right bundle branch block, and in another, a normal infantile pattern. High P waves were present in three of the electrocardiograms. None of the tracings showed the incomplete right bundle branch block pattern considered more characteristic of the "diastolic overloaded" ventricle. Fluoroscopy of the heart was carried out on all the cases by the same observers who performed the physical examination and cardiac catheterization. The size of the heart by fluoroscopy varied from normal to Grade III hypertrophy. The hypertrophy was considered right ventricular in five cases and general in two. Of the four cases of pure infundibular stenosis, three showed concavity of the infundibulum and one showed a normal infundibulum and pulmonary artery segment. In one patient with both valvular and in-

TABLE 2.—*Catheterization Findings in Nine Cases of Pulmonary Stenosis with Left-to-Right Shunt* *

Case No.	Pressure, Mm. Hg							Saturation, per Cent							Shunt	
	R. A.	L. A.	R. V. Inflow	R. V. Outflow	P. A.	Ao.	S. A.	Gradient RVI-RVO-PA	SVC	IVC	R. A.	RVI	RVO	P. A.	Ao.	S. A.	L. to R., % TPF	R. to L., % TSF
1	10/3	....	100/5	30/5	30/10	100/65	110/65	70 0	58	..	50	52	70	70	85	85	50	27
2	5/2	....	30/2	30/2	10/3	.....	65/35	0 29	..	..	60	90	90	90	..	75	78	56
3	8/2	....	100/7	60/5	60/50	.....	90/60	40 0	58	..	63	63	75	74	..	92	41	Slight
4	12/5	....	100/8	75/5	63/35	.....	105/65	25 12	73	60	65	89	89	89	..	94	80	Slight
5	3/2	....	35/2	35/2	15/7	.....	95/65	0 20	67	63	65	80	82	80	..	97	44	0
6	5/0	....	50/3	20/8	20/10	.....	100/60	0 32	72	..	70	72	85	85	..	98	50	0
7	8/2	....	110/5	110/5	17/5	.....	95/65	0 93	68	..	78	78	79	83	..	97	33	0
8	10/5	12/6	115/5	30/5	.....	.....	130/70	85 ..	58	60	86	86	86	..	..	88	65	28
9	10/3	....	70/2	70/2	15/7	.....	100/75	0 55	75	70	83	84	85	83	..	90	35	0

* R. A., right atrium; L. A., left atrium; R. V., right ventricle; P. A., pulmonary artery; Ao., aorta; S. A., systemic artery; SVC, superior vena cava; IVC, inferior vena cava; RVI, right ventricular inflow tract; RVO, right ventricular outflow tract; L. to R., Left to right; R. to L., right to left; % TPF, per cent of total pulmonary flow; % TSF, per cent of total systemic flow.

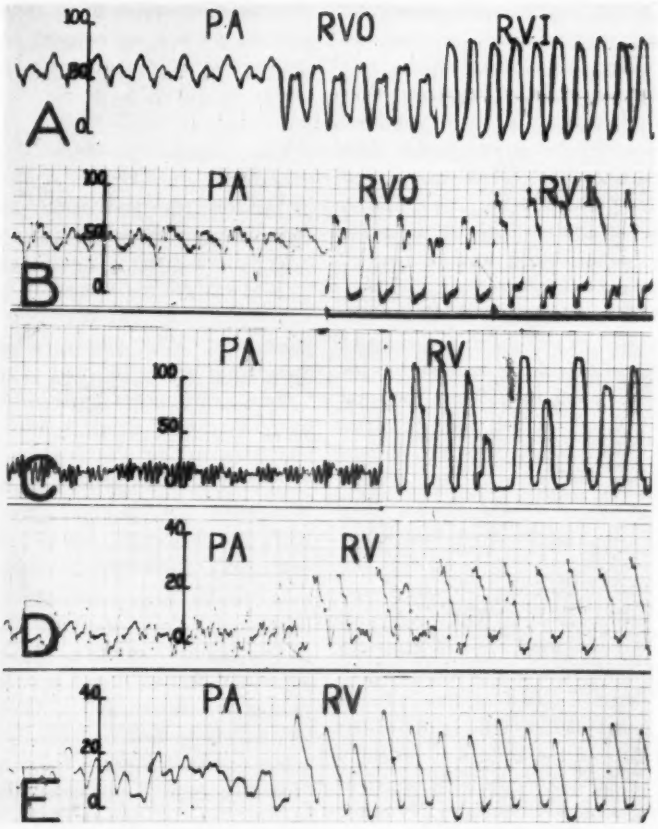


Fig. 2.—Some representative pressure tracings from the right ventricle and pulmonary artery. *A* (Case 3), ventricular septal defect with mild infundibular stenosis. *B* (Case 4), ventricular septal defect with pressure gradient in the outflow tract and across the pulmonary valve. *C* (Case 7), atrial septal defect with valvular pulmonic stenosis. *D* (Case 2), ventricular septal defect with mild valvular stenosis. *E* (Case 5), ventricular septal defect with mild pulmonary valvular stenosis.

fundibular stenosis the pulmonary trunk was dilated. In those cases with valvular stenosis the pulmonary trunk was dilated and pulsated prominently in three and was considered normal for the age of the patient in one. The pulmonary vascular shadows were of increased size in six cases, normal in two, and diminished in one. However, in all cases an increase in hilar vascular pulsation (from Grade I to Grade II) was noted. Figure 1 shows some representative chest roentgenograms from this group of cases.

Venous dye-dilution curves were performed on five patients and in each case showed evidence of left-to-right shunt; three of these showed additional evidence of slight right-to-left shunt. Oximetric records in two of the cases (Cases 2 and 8) showed marked respiratory variation in arterial oxygen saturation.

The exact anatomical diagnosis was not made in any of these cases prior to catheterization, though in three of the cases the diagnosis of pulmonary stenosis with left-to-right shunt was suggested prior to catheterization.

CATHETERIZATION FINDINGS

Catheterization was carried out by standard techniques under basal tribromoethanol (Avertin) anesthesia in the infants and

small children, at times supplemented by nitrous oxide-oxygen mixtures. In addition, a cuvette oximeter was used for rapid multiple or continuous catheter sampling with reinfusion of the blood in small children. Table 2 summarizes the catheterization data in these cases. The septal defect was entered by the catheter in four of the cases, and in the remaining cases the degree of arterialization of the venous blood was verified by repeated sampling of the areas in question. The shunt volume varied from 33% to 80% of the total pulmonary flow. In the cases of ventricular septal defect the average left-to-right shunt was equal to 57% of the total pulmonary flow, and in the cases of atrial septal defect, 44%. In all cases the pulmonary flow index was greater than normal and the pulmonary flow was greater than systemic flow. In two cases of ventricular septal defect and in one case of atrial septal defect there was definite right-to-left shunt, ranging from 28% to 56% of the systemic flow, and in two additional cases of ventricular septal defect there was probably a slight right-to-left shunt. In two of the cases of ventricular septal defect with right-to-left shunt over-riding of the aorta was probably present, since in both cases the right ventricular systolic pressures were considerably below systemic. In one of these cases the catheter passed easily into the aorta from the right ventricle and into a right-sided aortic arch. In two of the cases of ventricular septal defect the arterialization took place through a membranous septal defect into a low-pressure "infundibular chamber" distal to an area of infundibular stenosis.

The pulmonary stenosis was valvular in four cases, infundibular in four cases, and combined valvular and infundibular in one. Figure 2 shows some representative right ventricular and pulmonary artery pressure tracings. There was considerable variation in right ventricular systolic pressures and in right ventricular-pulmonary artery gradients. The mean gradient was 50 mm. Hg, with a range of 20 to 93 mm. Hg. The estimated pulmonary valve resistance was mild to moderate in most cases. In two of the cases of ventricular septal defect with pulmonary stenosis, pulmonary vascular resistance was also considerably increased.

COMMENT

The Clinical Syndrome.—Although in most of the cases of this syndrome reported in the literature and in our own cases the correct clinical diagnosis was not made prior to catheterization, it would appear that increased clinical awareness of this syndrome will result in a proper clinical diagnosis in most cases. Most observers have described these cases as having mild or no symptoms. Cyanosis was uncommon in the cases reported in the literature, although mild arterial oxygen unsaturation was present in a number at rest or after exercise. Our series demonstrates that the syndrome may be associated with any degree of cyanosis and in some cases with considerable disability.

It would be expected that if significant left-to-right shunt occurred in the presence of pulmonary stenosis the characteristic "diamond-shaped" harsh systolic murmur of pulmonary stenosis would tend to be exaggerated. Indeed, it is likely that the systolic murmur of atrial septal defect results largely from the high flow across the pulmonary valve. This is supported by the frequent finding of a thrill over the pulmonary artery at the time of surgical closure of atrial septal defects. In the case of ventricular septal defect it is more likely that the murmur results predominantly from flow with high pressure gradient across the defect, though some contribution to the murmur may arise from the high flow across the pulmonary valve. The diastolic murmur associated with atrial and ventricular septal defects is often present in this syndrome and may be helpful in its delineation, as diastolic murmurs are extremely rare in isolated pulmonary stenosis or in the tetralogy of Fallot. The early diastolic murmur, usually maximal in the second left interspace, is presumed to result from relative insufficiency of the pulmonary valve. A middiastolic murmur of lower pitch at the apex or lower left sternal border is presumed to result from the high flow across the mitral

or tricuspid valve in atrial or ventricular defects. The pulmonic second sound, usually increased in both atrial and ventricular septal defects and characteristically more widely split in the former, is usually diminished and single or absent in pulmonic stenosis.

What physical signs will predominate in any case will usually depend upon the relative dynamic importance of the two lesions. Rudolph and co-workers [7] have described the murmurs which they consider characteristic of pulmonary stenosis with left-to-right shunts. These findings were present in all but 1 of their 10 cases. In atrial septal defect with pulmonary stenosis, they describe a thrill at the second left intercostal space, a split but diminshed P_2, a rough systolic murmur at the second left intercostal space, and a middiastolic murmur at the apex. In ventricular septal defect with pulmonary stenosis, they describe a thrill at the third and fourth left intercostal spaces, decreased P_2, a rough systolic murmur at the second to fourth intercostal spaces, and a middiastolic murmur at the apex. The reported high incidence of the apical middiastolic murmur was not borne out by any of the other series in the literature, and this murmur was found in only one of our cases. However, we have found the early diastolic murmur at the left sternal border in all of our cases of atrial septal defect with pulmonary stenosis and in two of the cases of ventricular septal defect with pulmonary stenosis. The pulmonic second sound in our cases was of normal or increased intensity in all but one and single in all but one. A murmur considered characteristic of pulmonic stenosis was present in four.

The electrocardiograms in our cases showed "concentric" type of right ventricular hypertrophy in all but two of the cases. Most of the cases in the literature have shown the incomplete right bundle branch block pattern, less often the "concentric" type of right ventricular hypertrophy.

We feel that fluoroscopy of the heart is one of the most useful indices of the presence and degree of left-to-right shunt in these cases. In pure pulmonary stenosis of the valvular type it is usual to observe a dilated dynamic pulmonary trunk shadow with the pulsation often extending into the left pulmonary artery branches but always associated with quiet right hilar shadows. In all of our cases increased pulsation of the hilar vessels was noted. In the cases with marked infundibular stenosis there was concavity of the infundibular rgeion with pulsatile hilar shadows; we consider such a finding strongly suggestive of this disorder when seen in a noncyanotic person; among cyanotic congenital heart lesions there are several other malformations which may cause such findings.

Physiologic Considerations. — The catheterization data in our cases are similar to those reported in the literature on this syndrome. The pulmonary valve resistance was mild to moderate, and the volume of left-to-right shunt was usually moderate but at times was marked. In those cases with large left-to-right shunt the pulmonary valve resistance was only slightly increased. Two cases of ventricular septal defect with pulmonary stenosis showing significant venoarterial shunts had probable overriding of the aorta, as the resistance on the two sides of the circulation strongly favored a pure arteriovenous shunt. In two additional cases showing slight arterial oxygen unsaturation the right ventricular systolic pressure was approximately equal to the pressure in the systemic circuit. In the one case of atrial septal defect and pulmonary stenosis with moderate right-to-left shunt the pressure gradients in the two atria were such as to favor a left-to-right shunt slightly, but they were actually about equal during much of the cardiac cycle. The dynamics of both septal defects and pulmonic stenosis have been extensively discussed in the literature.

The dynamic significance of left-to-right shunts combined with pumonary stenosis has important practical implications in the consideration of cardiac surgery for such cases. It is apparent that closure of the septal defect will do much to decrease the systolic pressure and work load of the right ventricle, since the flow across the valve is related

to the square root of the pressure gradient. Prediction of the effect of opening the stenotic pulmonary valve on the degree of left-to-right shunt is not so simple. If the defect is large enough to offer essentially no resistance to flow, the flow will be determined by the relative resistance offered to flow on the two sides of the circulation, and decrease in the valve resistance would increase the degree of left-to-right shunt. However, in many of the cases it seems that the defect does offer resistance to flow and may be the limiting factor in determining the shunt volume.

Four of the patients reported in the literature were subjected to valvotomy; two showed improvement,* and two showed little change.[5] One of our patients (Case 7) had a pulmonary valvotomy performed elsewhere. There was a fall in right ventricular pressure and apparent clinical improvement, though we have had no opportunity to restudy the patient. One patient reported by Eldridge [8] had closure of an atrial septal defect with considerable improvement.

Lastly, it should be noted that some of the cases with large shunts and small right ventricular-pulmonary artery gradients probably represent relative pulmonary stenosis. As yet, we know of no absolute way of distinguishing the catheterization findings in such circumstances from those of mild organic pulmonic stenosis.

SUMMARY

Clinical and catheterization studies have been described in nine cases of pulmonary stenosis with increased pulmonary blood flow. There were six cases of ventricular septal defect with pulmonary stenosis and three cases of atrial septal defect with pulmonary stenosis; there were both valvular and infundibular stenoses. The clinical recognition and some of the dynamic implications of the syndrome are discussed.

* References 4 and 6.

REFERENCES

1. Abrahams, D. G., and Wood, P.: Pulmonary Stenosis with Normal Aortic Root, Brit. Heart J. **13**:519, 1951.

2. Gøtzsche, H.: Congenital Heart Disease, Copenhagen, The Author, 1952.

3. Deuchar, D. C., and Zak, G. A.: Cardiac Catheterization in Congenital Heart Disease: Four Cases of Pulmonary Stenosis with Increased Pulmonary Blood Flow, Guy's Hosp. Rep. **101**:1, 1952.

4. Broadbent, J. C.; Wood, E. H., and Burchell, H. B.: Left to Right Intracardiac Shunts in the Presence of Pulmonary Stenosis, Proc. Staff Meet. Mayo Clin. **28**:101, 1953.

5. Moffitt, G. R.; Zinsser, H. F., Jr.; Kuo, P. T.; Johnson, J., and Schnabel, T. G., Jr.: Pulmonary Stenosis with Left to Right Intracardiac Shunts, Am. J. Med. **16**:521, 1954.

6. Magidson, O.; Cosby, R. S.; Dimitroff, S. P.; Levinson, D. C., and Griffith, G. C.: Pulmonary Stenosis with Left to Right Shunt, Am. J. Med. **17**:311, 1954.

7. Rudolph, A. M.; Nadas, A. S., and Goodale, W. T.: Intracardiac Left to Right Shunt with Pulmonic Stenosis, Am. Heart J. **48**:808, 1954.

8. Eldridge, F. L., and Hultgren, H. N.: Pulmonary Stenosis with Increased Pulmonary Blood Flow, Am. Heart J. **49**:838, 1955.

9. Pollock, A. A.; Taylor, E. B.; Odel, H. M., and Burchell, H. B.: Pulmonary Stenosis Without Septal Defect, Proc. Staff Meet. Mayo Clin. **23**: 516, 1948.

10. Dow, J. W.; Levine, H. D.; Elkin, M.; Haynes, F. W.; Hellems, H. K.; Whitenberger, J. W.; Ferris, B. G.; Goodale, W. T.; Harvey, W. P.; Eppinger, E. C., and Dexter, L.: Studies of Congenital Heart Disease: Uncomplicated Pulmonary Stenosis, Circulation **1**:267, 1950.

11. Hull, E.: The Cause and Effect of Flow Through Defects of the Atrial Septum, Am. Heart J. **38**:350, 1949.

12. Little, R. C.; Opdyke, D. F., and Hawley, J. C.: Dynamics of Experimental Atrial Septal Defects, Am. J. Physiol. **158**:241, 1949.

Evaluation of Oral Cholecystography in Liver Disease

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Gall-bladder visualization by the oral route depends on an adequate blood level of dye following its absorption, its removal and excretion by the liver, and its entrance into and concentration by the gall bladder. It has been frequently stated that cholecystography is contraindicated in liver disease with jaundice, for one cannot determine whether the failure of visualization is due to liver or to gall-bladder disease. This study, which correlates the serum bilirubin level, the retention of sulfobromophthalein (Bromsulphalein) dye, and gall-bladder visualization in 40 patients with varying degrees of liver disease is an attempt to clarify the problem.

PROCEDURE

Forty patients with varying degrees of impaired liver function were selected for study. Tests of liver function and oral cholecystography were performed the same morning. Six tablets of iopanoic acid U. S. P. (Telepaque) were given the preceding evening. The sulfobromophthalein method consisted of the intravenous administration of 5 mg. of dye per kilogram, with removal of the blood specimen in 45 minutes. When the gall-bladder did not visualize, the determination was usually repeated within one week with use of 12 tablets of iopanoic acid. Occasionally 12 tablets of dye were given the first time. The gall-bladder filling was classified as good, poor, or none.

RESULTS

The results in terms of gall bladder visualization are presented in Tables 1 to 3, with the patients listed according to the level of sulfobromophthalein retention. Serial results in five patients are shown in Table 4.

TABLE 1.—*Good Gall-Bladder Visualization*

Case	Sulfobromophthalein Retention, %	Serum Bilirubin, Mg./100 Ml. Direct	Total	Diagnosis
1	2	0.38	0.58	Papilloma of gall bladder
2	5	Neg.	0.68	Splenomegaly, cause ?
3	5	0.19	0.96	Cholelithiasis
4	7	0.19	0.77	Cholelithiasis, hepatomegaly
5	9	0.19	1.51	Schistosomiasis of liver
6	9	0.19	0.96	Portal cirrhosis
7	9	0.77	1.77	Toxic hepatitis
8	9	Neg.	0.38	Cholelithiasis
9	10	0.38	2.50	Infectious hepatitis
10	10	Neg.	0.68	Hematemesis, cause ?
11	13	1.60	3.20	Infectious hepatitis
12	14	0.77	2.30	Infectious hepatitis
13	14	0.14	1.10	Chronic myelogenous leukemia
14	15	0.19	0.38	Disseminated lupus erythematosus
15	17	0.18	1.20	Bronchopneumonia, hepatomegaly
16	19	0.87	2.12	Infectious hepatitis
17	19	0.28	1.38	Subacute infectious hepatitis
18	22	0.19	0.96	Portal cirrhosis
19	23	0.25	0.52	Portal cirrhosis
20	24 *	0.19	1.69	Fatty liver
21	25	1.89	2.60	Infectious hepatitis
22	25	0.71	2.60	Infectious hepatitis
23	26	0.20	1.08	Acute intermittent porphyria
24	29	0.29	1.10	Infectious mononucleosis
25	36	2.30	5.20	Infectious hepatitis
26	47 *	2.71	7.14	Infectious hepatitis

* Double dose of dye.

TABLE 2.—*Poor Gall-Bladder Visualization*

Case	Sulfobromophthalein Retention, %	Serum Bilirubin, Mg./100 Ml. Direct	Total	Diagnosis
1	21	0.10	0.38	Infectious mononucleosisis
2	27	1.70	4.20	Infectious hepatitis
3	29 *	1.10	3.00	Infectious hepatitis
4	35	0.77	2.87	Chronic hepatitis
5	43 *	1.40	2.50	Chronic hepatitis
6	48 *	4.60	13.6	Chlorpromazine hepatitis
7	53	....	11.0	Infectious hepatitis
8	55	1.60	4.40	Infectious hepatitis

* Double dose of dye.

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TABLE 3.—*No Gall-Bladder Visualization*

Case	Sulfobromophthalein Retention, %	Serum Bilirubin, Mg./100 Ml. Direct	Total	Diagnosis
1	18 *	0.96	2.50	Cholelithiasis
2	22	0.08	0.77	Hodgkin's disease, ? cholelithiasis
3	38 *	5.00	13.30	Infectious hepatitis
4	41 *	1.90	2.70	Disseminated lupus erythematosus
5	46	4.40	6.90	Cholelithiasis
..	9 *	0.86	2.50	.....

* Double dose of dye.

TABLE 4.—*Serial Studies*

Case	Sulfobromophthalein Retention, %	Serum Bilirubin, Mg./100 Ml. Direct	Total	Diagnosis	Gall-Bladder Visualization
1	38 *	5.00	13.30	Infectious hepatitis	None
..	36	2.30	5.20	.....	Good
2	47 *	2.71	7.14	Infectious hepatitis	Good
..	25	1.50	3.51	.....	Poor
..	12	1.30	2.90	.....	Good
3	48 *	4.60	13.60	Chlorpromazine hepatitis	Poor
..	28 *	0.77	2.60	.....	Good
4	55	1.60	4.40	Infectious hepatitis	Poor
..	20	0.84	1.28	.....	Good
5	46	4.40	6.90	Cholelithiasis	None
..	9 *	0.86	2.50	.....	None
..	49 *	2.80	3.80	.....	None
..	10 *	0.64	1.70	.....	None

* Double dose of dye.

There was good gall-bladder visualization in 26 of the 40 patients. The maximum sulfobromophthalein retention, 47%, and the highest serum bilirubin value, 7.14 mg. per 100 ml., occurred in a patient with acute hepatitis who had received a double dose of dye. Serial studies in this case (Table 4) showed poor visualization with a single dose of dye when the serum bilirubin was 3.51 mg. per 100 ml. and the sulfobromophthalein retention was 25%. In the following week, when the total serum bilirubin was 2.19 mg. and the sulfobromophthalein retention was 12%, there was good visualization with a single dose of dye. The gall-bladder was well visualized in nine patients whose sulfobromophthalein retention was over 20%.

There were eight patients in whom there was poor gall-bladder visualization. Still, visualization was sufficiently adequate to rule out the presence of cholelithiasis. Three patients received a double dose of dye. The sulfobromophthalein retentions in all instances were above 20%. The serum bilirubin value tended to be higher than in the well-visualized group, but it was normal in one instance. Repeat studies (Table 4) in two patients revealed good visualization as the serum bilirubin and sulfobromophthalein levels were returning toward normal values.

There was no gall-bladder visualization in five patients. Repeated studies on five occasions were performed in the patient with disseminated lupus erythematosus (Table 4), and there was no visualization each time. Serial studies in one patient with infectious hepatitis (Table 4) showed good visualization when the sulfobromophthalein level fell from 38% to 36% and the total serum bilirubin level fell from 13.30 to 5.20 mg. per 100 ml. Two patients had proved cholelithiasis, whereas in one the history was suggestive of this diagnosis. Studies were performed in four consecutive weeks for one patient whose admission diagnosis was infectious hepatitis (Table 4). Despite variations in the sulfobromophthalein retention from 9% to 46% and in the total serum bilirubin from 1.70 to 6.90 mg. per 100 ml., there was no gall-bladder visualization. At operation cholelithiasis and choledocholithiasis were found.

The sulfobromophthalein retention correlated more closely with the degree of gall-bladder visualization than did the serum bilirubin level.

Previously unsuspected cholelithiasis was found in four patients and was the cause of the jaundice in two of them.

There were no serious or unusual side-effects from either the gall-bladder or the sulfobromophthalein dye.

COMMENT

Since the introduction of oral cholecystography in 1924,[1] seven publications * have dealt with either gall-bladder visualization in liver disease or its use in differentiating intrahepatic from extrahepatic causes of

* References 2-8.

jaundice. The relationship between sulfobromophthalein retention and gall-bladder visualization in these articles is presented in Table 5.

Rudisill in 1930 [2] was the first to report on gall-bladder visualization in jaundiced patients. He described good gall-bladder visualization in seven of eight cases with hepatitis. The gall-bladder was visualized well in one jaundiced patient with cholelithiasis and did not visualize in another with carcinoma of the common bile duct. Serum bilirubin and sulfobromophthalein bromophthalein retentions and whose gall bladders did not visualize. The authors concluded that a nonvisualized gall bladder in a patient with sulfobromophthalein retention below 25% indicated gall-bladder disease, whereas with retentions above this level liver disease might be the cause of the nonvisualization. Foley in 1933 [4] discussed a jaundiced patient who was first thought to have extrahepatic disease but in whom the diagnosis was changed to intrahepatic disease when his gall bladder visualized well. Without giving laboratory data, he described

TABLE 5.—*Relationship Between Sulfobromophthalein Retention and Gall-Bladder Visualization*

Author	Patients, No.	Diagnosis	Sulfobromophthalein Retention, %	Gall-Bladder Visualization		
				Good	Poor	None
Rudisill (1930)	8	Hepatitis	*	7	0	1
Blomstrom & Sandstrom (1932)	37	Hepatitis	Above 30	1	6	13
			Below 30	17	0	0
	24	Cholelithiasis and carcinoma of gall bladder	Above 40	0	0	13
			Normal	0	0	11
Foley (1933)	16	"Medical" jaundice	*	8	3	5
	13	"Surgical" jaundice	*	0	0	13
Readinger (1950)	43	Viral hepatitis	(A) Below 30 in 30 pts.	(A)	(B)	(C)
			(B) Above 30	31	3	9
			(C) Above 30 in 7 pts.			
Jarvinen & Paltia (1952)	19	Hepatitis	*	15	3	1
	19	Portal cirrhosis	*	0	6	13
Cuniff (1953)	50	Portal cirrhosis	* (D) (E) (F)	(D)	(E)	(F)
			0-20: 7 11 6 pts.	14	20	16
			21-30: 2 3 4 pts.			
			Above 30: 1 1 4 pts.			
Etess & Straus (1953)	35	Cirrhosis hepatitis, miscellaneous liver disease	(G) Below 20	(G)	(H)	(I)
			(H) 20-23	23	5	7
			(I) Above 23			

* Complete data not given.

levels were not included in this publication. Blomstrom and Sandstrom in 1932 [3] performed cholecystography and sulfobromophthalein studies in 68 patients with liver disease. The dose of sulfobromophthalein dye was 2 mg. per kilogram, and the blood sample was withdrawn in 30 minutes. Of the 37 patients with hepatitis, 19 of 20 with sulfobromophthalein retention above 40% had poor or no gall-bladder visualization. Seventeen patients with sulfobromophthalein retentions below 30% had good gall-bladder visualization. There were 11 patients with cholecystitis, cholelithiasis, or carcinoma of the gall bladder who had normal sulfo-

16 patients with "medical" jaundice in whom there was good gall-bladder visualization in 8, poor in 3, and none in 5 patients. There was no gall-bladder visualization in 13 patients who had "surgical" jaundice. Readinger and co-workers in 1950 [5] determined the incidence of gall-bladder visualization in 43 patients with viral hepatitis. There was good visualization in 31 patients, poor in 3, and none in 9. A double dose of dye was used in 10 patients. The sulfobromophthalein was above 30% in one of the well-visualized cases, in all of the poorly visualized cases, and in seven of the nonvisualized cases. There was good gall-bladder

visualization in 29 of the 32 patients whose sulfobromophthalein retention was below 30%. Eight of the nine patients whose gall bladders did not visualize on the first examination showed good visualization as the severity of their disease decreased. There was good gall-bladder visualization in 33 of 36 patients whose total serum bilirubin was below 11 mg. per 100 ml. and in 1 patient whose serum bilirubin was above this level. The authors advised the use of a double dose of dye when the serum bilirubin was over 5 mg. per 100 ml. or the sulfobromophthalein retention greater than 15%. Jarvinen and Paltia in 1952 [6] attempted to differentiate portal cirrhosis from acute and subacute hepatitis by cholecystography. The patients had only slight serum bilirubin elevations. In 19 patients with hepatitis there were 15 instances of good, 3 of poor, and 1 of no gall-bladder visualization. In 19 patients with cirrhosis there was poor visualization in 6 patients and none in 13. The authors felt that in the presence of mild jaundice of intrahepatic disease a nonvisualized gallbladder would suggest cirrhosis rather than hepatitis. Cuniff and co-workers in 1953 [7] performed cholecystography in 50 cirrhotic patients who were not jaundiced. There was good gall-bladder visualization in 14 patients, poor in 20, and none in 16. The gall bladder was well visualized in 1 of the 12 patients with ascites. Unsuspected cholethiasis was found in nine subjects. The visualization could be correlated with the clinical status of the patient and the degree of sulfobromophthalein retention. The gall bladder was visualized in one of eight patients whose bromsulphalein retention was over 30%. The patients whose total serum bilirubin was above 3 mg. per 100 ml. rarely had good gall-bladder visualization. As the patient's clinical status improved, the incidence of gall-bladder visualization increased. Etess and Straus in 1953 [8] correlated gall-bladder visualization with sulfobromophthalein retention in nonjaundiced patients with liver disease. The gall-bladder visualized well in 23 patients whose sulfobromophthalein retention was below 20%, poorly in 5 patients whose sulfobromophthalein retention was between 20% and 23%, and not at all in 7 patients whose sulfobromophthalein retention was above 23%. They described two patients whose gall bladders visualized well when their sulfobromophthalein retentions were below 20% and did not visualize when their sulfobromophthalein retentions rose to between 28% and 30%. They concluded that gall-bladder disease was the likely cause for a nonvisualized gall bladder in a patient whose sulfobromophthalein retention was below 20%.

The results described in the seven articles generally agree with those of the present study and are summarized as follows:

1. Cholecystography does not result in adverse side-effects in the patient with liver disease. 2. The serum bilirubin level and the degree of sulfobromophthalein retention are the liver-function tests which can be best correlated with gall-bladder visualization. 3. The gall bladder should visualize in hepatitis of any cause when the sulfobromophthalein retention is below 20% and the serum bilirubin is below 5 mg. per 100 ml. Visualization may occur with serum bilirubin levels up to 11 mg. per 100 ml. and sulfobromophthalein retentions up to 30%. 4. Gall-bladder visualization in portal cirrhosis can be correlated with the sulfobromophthalein retention as in patients with acute hepatitis. A serum bilirubin level above 5 mg. per 100 ml., a level lower than in many patients with hepatitis, usually means that the gall bladder will not be visualized. 5. Serial studies and a double dose of dye are recommended when the gall bladder does not visualize. If the gall bladder still does not visualize as the tests of liver function fall, gall-bladder disease must be suspected. A double dose of dye is recommended in the presence of marked jaundice. 6. It is generally the degree and not the type of liver abnormality which is important in determining whether the gall bladder will or will not visualize. Sulfobromophthalein retention below 20% and serum bilirubin levels below

5 mg. per 100 ml. should not interfere with gall-bladder visualization, while values above this level may or may not interfere.

We have had no experience with the intravenous administration of gall-bladder dye, but it is probable that this would give an even greater incidence of visualization in the patient with liver disease.

SUMMARY AND CONCLUSIONS

This study correlates the serum bilirubin level, the retention of sulfobromophthalein (Bromosulphalein) dye, and gall-bladder visualization in 40 patients with hepatic disease. The literature on this topic is reviewed and summarized.

The presence of liver disease with jaundice is not a contraindication to cholecystography.

It is the degree and not the type of hepatic disease which determines whether the liver can extract the dye from the blood stream and transfer it to the biliary tract.

Though rigid rules cannot be established, a sulfobromophthalein retention below 20% and a total serum bilirubin value lower than 5 mg. per 100 ml. should not interfere with gall-bladder visualization. Sulfobromophthalein levels from 20% to 30% and serum bilirubin values from 5 to 10 mg. per 100 ml. may or may not interfere with gall-bladder visualization. Values above these levels usually interfere with good gall-bladder filling.

Serial studies with a double dose of dye are recommended when the gall bladder does not visualize. If visualization does not occur as the liver-function tests return toward normal, the likely cause is extrahepatic disease. The failure of gall-bladder visualization in mild or moderate hepatic disease suggests an extrahepatic cause for nonvisualization. Used in this fashion, oral cholecystography may be helpful in differentiating extrahepatic from intrahepatic causes of jaundice.

Unsuspected cholelithiasis may be found as the cause for or concomitantly with the liver disease if cholecystography is performed more frequently in the jaundiced patient.

REFERENCES

1. Graham, E. A., and Cole, W. H.: Roentgenologic Examination of the Gallbladder, J. A. M. A. **82**:613-614, 1924.

2. Rudisill, H., Jr.: Gallbladder Visualization in Jaundiced Patients, J. A. M. A. **95**:1425, 1930.

3. Blomstrom, H., and Sandstrom, C.: On Cholecystography in Cases of Impaired Liver Function, Acta. chir. scandinav. **71**:135-149, 1932.

4. Foley, E. F.: Cholecystography in Jaundice, M. Clin. North America **17**:467-472, 1933.

5. Readinger, H. M.; Swift, W. E., Jr.; Gardiner, H. T., and Sheedy, J. A.: Oral Cholecystography in Patients with Viral Hepatitis, Am. J. Med. **8**:611-613, 1950.

6. Jarvinen, K. A. J., and Paltia, V. E.: Differential Diagnosis of Hepatitis and Liver Cirrhosis by Means of Cholecystography, Am. J. Digest. Dis. **19**:244-247, 1952.

7. Cuniff, C. L.; Dolan, M. A., and Leevy, C. M.: Cholecystography in Portal Cirrhosis Without Jaundice, Gastroenterology **25**:557-564, 1953.

8. Etess, A. D., and Straus, B.: Cholecystography in the Presence of Liver Disease, New England J. Med. **249**:930-932, 1953.

Treatment in Internal Medicine

THE TREATMENT OF CIRRHOSIS OF THE LIVER

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CIRRHOSIS of the liver represents a chronic disease caused by serious parenchymal damage to the liver, usually of long-continued or repetitive type, in which malnutrition is usually regarded as an important accompanying and predisposing etiological factor. Because of its vital and widely diversified metabolic functions, the liver is commonly exposed to a variety of damaging agents in the form of toxic chemicals, infections, circulatory disturbances, and systemic metabolic abnormalities, but the nutritional state of the organism is believed to act as a basic underlying factor which is capable of conditioning susceptibility or resistance to cellular injury. The specificity of essential nutrients in the defense against liver damage is poorly defined except for the high protective function of protein of excellent biological value and, possibly, for the "methyl donor compounds" choline and methionine, both of which are present in normally adequate amounts in a well-balanced protein ration.

Many classifications of hepatic cirrhosis have been proposed in the past, most of which are acceptable for general clinical orientation. The major forms which constitute, quantitatively, the most important therapeutic problems in the United States are the following: (1) Laennec's, or portal, cirrhosis; (2) postnecrotic cirrhosis, and (3) biliary or obstructive cirrhosis. Much rarer in incidence in this country are (4) parasitic cirrhosis, (5) pigmentary cirrhosis, and (6) hepatolenticular degeneration; (7) cardiac or congestive cirrhosis and (8) syphilitic cirrhosis are special forms which depend upon the presence of coexisting disease, and the management of these depends, to a large extent, upon successful treatment of the underlying conditions. Special mention should be made, in passing, of the tropical form of malignant malnutrition known as kwashiorkor, which is indigenous to certain areas of Africa. It is characterized by serious and even fatal liver damage with cirrhosis and is due to the use of poor diets which are strikingly deficient in protein of high nutritional value. In many ways, certain basic principles underlie the therapeutic approach to all types of liver-cell injury, and this summary will, therefore, deal primarily with the commonest of these diseases, portal, or Laennec's, cirrhosis.

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BASIC PRINCIPLES UNDERLYING THERAPY

Laennec's cirrhosis, in the past, has often been designated as "alcoholic cirrhosis" because of the frequent, but by no means invariable, association of the disease with chronic alcoholism. During the past 18 years a multidisciplinary attack on the problems of hepatic metabolism has resulted in an accumulation of impressive evidence, both experimental and clinical, which, in general, relegates alcohol to a secondary position as an etiological factor, subordinate to malnutrition, especially in regard to good quality protein and a number of vitamins and related nutrients. There remains, however, some evidence and opinion to suggest that the toxic action of ethyl alcohol may be important in the production of liver damage.[1] From the practical standpoint at present, therefore, in addition to the prohibition of alcoholic beverages, the major therapeutic effort is directed toward the reestablishment of an optimal state of nutrition.

The modern era of treatment was ushered in by the important report of Patek in 1937 [2] and by his subsequent paper four years later [3]

describing striking improvement in cirrhotic patients from the use of a nutritious diet which contained generous amounts of protein and carbohydrate and moderate amounts of fat, supplemented with crude preparations of the vitamin-B complex. This work represented the application to liver disease of a large volume of earlier clinical work * which had clearly demonstrated that the pathogenesis of pellagra, polyneuritis, and beri-beri heart disease depended upon nutritional deficiency, whether alcoholism was present or not. The frequent association of cirrhosis with alcoholism and poor dietary habits, together with the common coexistence of deficiency manifestations in that disease, provided a logical correlation which had not previously been explored. This basic concept of hepatic cirrhosis as a nutritional deficiency state was further substantiated by an enormous body of experimental evidence in animals, which had somewhat clarified the importance of various dietary components in the production or prevention of liver injury and cirrhosis. Subsequent clinical studies have now provided an adequate fund of information to establish very clearly the malnutrition basis of hepatic cirrhosis and have allowed the formulation of an effective and generally acceptable therapeutic program in this disease.

Interest in the importance of lipotropic dietary factors probably dates back chiefly to the reports of Connor in 1938 [8] and 1939,[9] calling attention to the frequent occurrence of fatty infiltration of the liver in the course of both diabetes mellitus and chronic alcoholism. The fat-mobilizing action of choline was already known at that time through the work of Best and his associates,[10] but further study of these dietary interrelationships was reported by Gyorgy and Goldblatt,[11] with subsequent establishment of choline as a lipotropic agent of practical value in the clinical management of cirrhotic patients.[12] A similar lipotropic function of the essential sulfur-containing amino acid, methionine, was described by Tucker and Eckstein in 1937,[13] and supplementation by this compound has since been observed to parallel the action of choline, in both animals and humans.† Both of these nutrients are believed to exert their protective effect as "methyl" donors or as transmethylating agents, and it has been suggested that the beneficial value of high-protein diets in the therapy of hepatic cirrhosis may be related, in part at least, to their content of methionine or choline or both.

An additional and more recent chapter in the story of lipotropic agents was written by Du Vigneaud and his group in 1945 [17] in work which demonstrated the capacity for synthesis of methyl groups in the animal body. A large volume of subsequent experimental work has further elucidated the mechanism of biosynthesis of methyl groups, with the clear indication that both cyanocobalamin (vitamin B_{12}) and folic acid (folacin) are involved.[18] Thus, the choline requirement for growing rats is significantly lowered when cyanocobalamin is included in the ration, in the presence of homocystine (an unnatural amino acid) as a methyl acceptor. According to this concept, the "methyl pool" for metabolic processes depends upon both the dietary supply of preformed methylated compounds, chiefly in the form of choline and methionine, and a supplementary contribution from endogenous synthesis. In experimental animals the latter source alone does not appear to be adequate for all metabolic needs, and it may be presumed that the same holds true in humans. The clinical implications of these experiments may be inferred, even though definitive studies in human cirrhosis have not determined the roles of cyanocobalamin and folic acid in the program of treatment. Nevertheless, it has been suggested that the therapeutic value of intravenously administered crude liver extract, shown by Labby, Shank, Kunkel, and Hoagland [19] to be an effective agent for restoration of appetite and protein storage, may be due to its content of cyanocobalamin. It is interesting to speculate, how-

* References 4-7.

† References 14-16.

ever, that serious liver damage with fatty infiltration and cirrhosis is not commonly an important part of the clinical picture of pernicious anemia, in which inability to absorb cyanocobalamin is recognized as a major pathogenic feature.

During the years since 1944, wide and prolonged experience by clinicians in the practical use of choline and methionine has now provided additional perspective which indicates that lipotropic dietary factors, despite their proved fat-mobilizing action, do not contribute any significant therapeutic advantage over that obtained from diets rich in biologically high-quality protein. Accordingly, their use has been largely abandoned, and most clinics and hospitals now employ dietary management unsupplemented by lipotropic agents.

SODIUM RESTRICTION

One of the important recent contributions to an understanding of hepatic cirrhosis, as well as other forms of liver injury, has been the discovery of a complicated metabolic and humoral cause of fluid retention, edema, and ascites, previously regarded as largely an osmotic phenomenon due to diminished serum albumin, augmented by a mechanical factor secondary to intrahepatic interference with portal blood flow with consequent rise in portal blood pressure. An anomaly of fluid balance coincident with liver damage had been recognized for many years, as described by Gilbert and Lerevoullet,[20] Ratnoff and Patek,[21] and Adlersberg and Fox [22] in cirrhosis and by Jones and Eaton [23] in infectious hepatitis, but the mechanism of this fluid retention in chronic liver disease was first studied in detail by Ralli and her associates in 1945.[24] Their findings indicated the presence of excessive amounts of an antidiuretic substance in the urine of cirrhotic patients with ascites. It was postulated by the authors that the source of this material might be the posterior pituitary gland.

Of equal importance and undoubtedly correlated with the problem of water retention in liver disease is the old observation that these patients have a seriously impaired renal capacity to excrete sodium. This phenomenon has been intensively investigated in recent years ‡ and is characterized by augmented renal tubular reabsorption of the sodium ion with a similar, but disproportionately less, effect upon chloride, resulting in a consistent fall of the Na/Cl ratio in urine. Further study of the mechanism of this effect has shown it to be produced, to a large extent at least, by the accumulation of excessively large amounts of a sodium-retaining steroid compound arising from the adrenal cortex, recently identified as aldosterone, or a derivative of it.§ It seems apparent that a close relationship must exist between the adrenal salt-retaining potential and the hypothalamic-pituitary mechanism, although no one, to date, has been able to demonstrate conclusively the basic means of control of these vital homeostatic functions. Body fluid concentrations of sodium and/or potassium, circulating plasma volume, and total osmolarity of blood, all have been suggested as critical "triggering" values for activating these humoral functions, but, at this writing, none seems to be entirely satisfactory. In any case, the neuroendocrine system, through mechanisms not yet understood, exerts homeostatic control over water and electrolyte balance, and the disturbance in this function seen in cirrhosis of the liver may possibly be regarded as compensatory for a constant dehydrated, hypo-osmolar state in the circulating blood, despite persistent sodium and water accumulation. The excessive quantities of aldosterone recoverable in the urine may represent adrenal cortical overproduction as a result of pathological stimulation or may be due to decreased hepatic destruction of circulating active hormone brought about by hepatocellular damage. There is experimental evidence which tentatively supports the latter possibility as a contributing factor,[32] but, in any case, the aldosteronism must be regarded as secondary to some unknown trigger mechanism, one component of which would seem to be either hyponatremia or hypo-osmolarity of blood,

‡ References 25-28.
§ References 29-31.

since both of these values commonly or regularly are found to be depressed coincidently with sodium and fluid retention. The interrelationship between posterior pituitary and adrenal cortical functions has been described by Harris and co-workers.[33] Further clarification of the high aldosterone titers in this disease, as a primary or secondary factor in the development of ascites, is urgently needed if a rational therapeutic approach is to be devised.

Limitation of salt intake has been a standard item of treatment in hepatic cirrhosis ever since the significance of sodium retention was recognized. Eisenmenger and associates [26] observed a critical level of salt intake at 1.2 gm. daily, above which ascites regularly recurred. Later work by the same group [34] provided evidence of electrolyte changes in saliva, sweat, blood, and urine which strongly suggested that the abnormal sodium retention in cirrhosis is largely a humoral phenomenon acting by way of the renal tubule. Therapeutic measures designed to counteract this metabolic anomaly have now become widely accepted and consist of a nutritious low-sodium diet and the use of various natriuretic agents such as carbonic anhydrase inhibitors and mercurial diuretics. An excellent discussion of the pathogenesis and management of ascites is available in the Combined Staff Clinic report from Presbyterian Hospital in New York.[35]

Closely related to the disturbances of fluid and electrolyte balance in cirrhosis is the problem of serum protein levels and the therapeutic use of diuretic agents. Based upon the now abandoned belief that antidiuresis in this disease results primarily from diminished osmotic pressure within the vascular compartment as a consequence of inadequate amounts of circulating protein, especially albumin, several investigations during recent years were designed to provide further practical information. Thorn and co-workers [36] in 1946, using intravenously administered salt-poor human serum albumin over periods up to 10 days, reported significant improvement in the urine volume and serum protein values, and nitrogen balance studies indicated retention of approximately 80% of the albumin supplement. It should be noted, however, that salt intake was restricted to 1 to 2 gm. daily during the period of study, and good diets with vitamin supplements were also provided. It is possible, therefore, that some of the diuresis may have been produced by factors other than the rise in serum albumin. A later study by Faloon and associates [37] confirmed these findings, but the value of a sodium-poor diet (500 mg. daily) was also found to be significant in retarding ascites formation. The authors concluded that the relative importance of hypoalbuminemia and of portal hypertension in the genesis of ascites could not be defined; consequently, we may now feel justified in believing that serum protein alterations constitute one of several factors to which may be attributed the failure of water and sodium excretion in cirrhosis.

The application of various diuretic agents to the problem of ascites is a natural consequence of the clinician's desire to move a large accumulation of fluid which is mechanically distressing and therapeutically deleterious because of its interference with appetite and visceral circulatory relationships. Furthermore, this fluid has been shown to be metabolically active, in a state of dynamic equilibrium with other body fluid compartments, rather than a sequestered, inert reservoir.[38] Many clinical studies bearing on diuretic therapy have been reported || indicating the improvement in water and sodium excretion which follows the use of diuretics, especially the mercurials when their action is potentiated by ammonium chloride. The resulting urinary loss of electrolyte is usually maximum for chloride and great for sodium, and there may often be heavy loss of potassium, even to the production of manifestations of hypokalemia, such as lassitude, drowsiness, and muscular weakness. Sodium depletion, likewise, may complicate vigorous and persistent antidiuretic therapy, particularly when it is combined with a rigorous

|| References 37 and 39.

low-sodium diet and repeated paracenteses, each of which may remove several hundred milliequivalents of sodium. The onset of hyponatremia is usually accompanied by a refractory state toward diuretic agents. It is of great importance, therefore, that blood electrolyte levels be followed very carefully, if complications are to be avoided.

COMPLICATIONS

A. Upper Gastrointestinal Bleeding.—The occurrence of esophageal varices, often extending into the cardiac portion of the stomach, is a result of increased portal pressure, usually secondary to intrahepatic vascular obstruction, with the varicosities representing one of the several collateral channels which may arise to circumvent the obstruction. Bleeding is most commonly of a massive type and is often extremely serious or even fatal. Danger of this disaster is greatly augmented by the common coexistence of poor coagulability of the blood, secondary to a lowered prothrombin content, which, when unresponsive to the parenteral administration of vitamin K, is indicative of serious hepatocellular damage. On the basis of the same anatomical and physiological considerations, bleeding may take the form of chronic, slow oozing with the production of profound anemia of blood loss. The latter form is relatively much less common than the former, but bleeding of any type demands treatment which may involve both medical and surgical measures. Massive hemorrhage is an emergency problem, which is most frequently managed by the insertion of an inflatable balloon into the esophagus or stomach or both. Injection of the varices with sclerosing solutions has been attempted but, in general, has been less satisfactory. Portacaval shunt operations of various types, as described by Blakemore,[40] by Linton,[41] by Rousselot,[42] and by others are now being generally used for the purpose of relieving the intrahepatic block and reducing the pressure in the portal system. Choice of the specific type of procedure is outside the scope of the present discussion.

B. Hepatic Coma.—This complication is usually a near-terminal event and frequently ends fatally. It is known to occur in both progressive and well-stabilized, but advanced, chronic liver disease, but the usual manifestations of advanced liver failure are not always present when coma appears. The premonitory signs of impending hepatic failure, as described by Adams and Foley,[43] consist of mental confusion, a characteristic tremor, and specific electroencephalographic changes, leading to a progressive state of stupor, coma, and death. The underlying metabolic disturbances have been studied by Snell and Butt[44] and are characterized by elevated blood levels of pyruvate and lactate, which may be related to inadequate supply or utilization of thiamine. There is also an accumulation in blood and tissues of ammonia, as described by Traeger, Gabuzda, Ballou, Schwartz, Phillips, and Davidson,¶ ascribed by these authors to a serious disturbance in protein metabolism in which the hepatic conversion of ammonia to urea is impaired, with a resulting rise in blood concentrations of the former. Despite these findings, the correlation between chemical and clinical findings is not sufficiently close to justify a definite causal relationship between ammonia and hepatic coma. It is logical, however, that the ingestion of excessively large amounts of protein food in patients with borderline hepatic function may precipitate a state of impending coma.

Furthermore, the therapeutic use of large, or even usual, doses of some drugs may induce a response of similar type, owing to the diminished capacity of the damaged liver to detoxify or metabolize these compounds at a normal rate. Of particular importance in this regard are morphine and its derivatives and the barbiturates.

The treatment of hepatic coma, whether fully developed or impending, depends therefore upon reduction of dietary protein, avoidance of dangerous drugs, maintenance of an adequate fluid intake with restriction or

¶ References 45 and 46.

administration of needed electrolytes according to the specific needs, the supplementation of the diet with large amounts of either glucose or fructose, and possibly the administration of glutamine and either corticotropin (ACTH) or cortisone. The use of glutamine is based upon its theoretical and demonstrable capacity to combine chemically with ammonia, but its practical clinical use has been very limited and is not especially promising. Rationale for the introduction of corticotropin and cortisone into the therapy of terminal liver failure is difficult to define. These hormones produce a detoxifying effect upon many naturally occurring noxious agents, not limited to the hepatotoxins, and they also are capable of nonspecifically suppressing the inflammatory reaction, which, however, is usually not present in this condition. On the other hand, one of the main metabolic effects of cortisone is to divert the main stream of protein metabolism from anabolism to deamination and glyconeogenesis. This change, induced by the extremely large doses (up to 1 gm. or more daily) of steroid usually advised in hepatic coma, would tend to increase rather than decrease the total volume of amino compounds and urea derived from endogenous metabolism. In my experience, temporary improvement in the clinical state of the patient often follows this form of therapy, but there remains considerable doubt that the ultimate clinical course and final outcome are significantly altered.

THE PROGRAM OF THERAPY

A specific plan of therapy of cirrhosis involves bed rest, the prohibition of alcoholic beverages, the providing of an attractively prepared nutritious diet, the sharp limitation of dietary sodium intake, the administration of antibiotics as needed to control intercurrent infection, the performance of paracentesis for control of marked ascites, and the use of mercurial diuretics as a supplement to other measures in the control of fluid and sodium retention. Special measures are needed to meet complicating and emergency situations as they arise. Each of these items will be discussed in detail.

Bed Rest.—Most patients with advanced liver disease will accept bed rest very willingly because of weakness, muscular wasting, lassitude, and the general debilitating effect of their disease. In addition, fever is often present, to increase the sense of illness and malaise. With clinical improvement incident to therapy many of these constitutional symptoms subside to a sufficient extent that a semiambulatory state becomes desirable. However, rest is of definite value in the decompensated state of cirrhosis, and there is even some evidence that physical activity may increase the rate of reaccumulation of ascites.

Diet.—The diet which is currently being used in the treatment of hepatic cirrhosis in most hospitals contains a daily ration of about 90 to 125 gm. of protein, with an average of about 100 gm., of which the major portion is animal protein of high biological quality. Its content of choline and methionine, as well as of all essential amino acids, is usually considered adequate to eliminate the necessity for specific supplementation with any of these nutrients in pure form. Carbohydrate is supplied in amounts varying between 250 and 350 gm., and the fat content, formerly maintained at a restricted level, is now provided in more or less unrestricted amounts of 100 to 125 gm., to bring the total caloric value of the diet up to 2200 to 3000 calories daily. The present "liver diet" of the University Hospitals contains 100 gm. of protein and sharply limited amounts of sodium, usually not exceeding 300 mg. daily.* The basic pattern of this diet for a 24-hour period is as follows:

Food	Amount	Protein, Gm.	Sodium, Mg.
Lonalac †	3 cups	24	27
Meat, fish, fowl	3 servings	42	150
Vegetables	3 servings	5	5-100
Fruits	2 servings	None	5-25
Cereal	1 serving	2	1-3
Breads	4 servings	8	20
Total		81	188-325

† Low-sodium milk (Mead Johnson).

* See References 52 to 55 for further information relative to low-sodium diets.

Supplementary additions may be made from the following list:

Food	Amount	Protein, Gm.	Sodium, Mg.
Cottage cheese	3 tablespoons	8	8
Gelatin	1 tablespoon	7	5
Egg yolk	one	3	14
Bread	one serving	2	5
Meat	30 grams	8	30
Lonalac	1 cup	8	9

A typical menu prepared according to this plan is as follows:

Breakfast	Lunch	Supper
Pineapple juice	Salt-free meat loaf	Salt-free roast beef
Salt-free cereal†	Boiled potato	Salad of salt-free cottage cheese and pear
Salt-free toast	Salt-free-squash	
Salt-free butter	Salt-free bread, 1 slice	Salt-free cookie
Jelly	Salt-free butter	Salt-free bread, 1 slice
Lonalac, 1 cup	Salt-free chocolate pudding	Salt-free butter
Coffee		Lonalac, 1 cup

8:00 p. m.
Fruit juice with 1 tablespoon of gelatin
Salt-free cookie

The main problem in the planning of low-sodium diets for use in chronic liver disease lies in the selection of proteins of high biological value which are not overloaded with sodium, since most animal products do not satisfy the latter criterion. Accordingly, a low-sodium milk product is a necessity for this purpose, for which Lonalac has served very successfully. Salt restriction is greatly facilitated by the use of special low-sodium foods of many types which are available on the market, and, in addition, the addition of extra salt in food preparation obviously must be avoided. Inasmuch as protein and sodium content are the two details of major importance, it is obvious that caloric value may be increased as needed, by the free addition of carbohydrate in the form of sweetening of foods and beverages and even the use of candy. The fat content also may be modified according to the diet philosophy of the individual clinician or the specific needs of individual patients, by the addition of salt-free butter, oil dressings, and salt-free gravies.

The problem of anorexia, so often encountered in patients with liver diseases of all types, must be taken into special consideration in the plan of management. It is obvious that the mere planning of a satisfactory, therapeutic diet is of little value unless it is actually eaten by the patient. The elimination of salt alone tends to make food unpalatable to many, if not most patients, and so the attractiveness and acceptability of the diet in all other respects becomes of unusual importance. Since limitation of fat content has been justifiably deemphasized in recent years, on the basis of clinical experiment and experience, and since the fat content of foods has a great deal to do with their palatability, there seems to be adequate reason for recommending "normal" fat content in the cirrhosis diet. In severely anorexic patients it may at times be desirable or even necessary to resort to the administration of a nutritious liquid diet by stomach tube until the appetite begins to return. Under more favorable circumstances, when actual nausea and vomiting are not present, it is sometimes desirable to provide assistance to the patient, by nurses or attendants, in urging the acceptance of more food or in help with the simple mechanics of eating a meal. In any case, since diet constitutes the keystone of therapy, it is apparent that close cooperation between the medical, nursing, and dietetic personnel assumes an unusual importance, which is encountered in few other diseases.

By conscientious attention to these dietary principles, not only during hospitalization but also as a long-continued therapeutic regimen incorporated into the patient's pattern of living after discharge, remarkable improvement may be expected in many, if not most, patients with cirrhosis, excluding perhaps only those persons who are in a terminal or near-terminal stage of disease or who have limitation of life expectancy

† The University Hospitals have used, for the past year, a new cereal product called Sturdiwheat (or V-932), soon to be marketed under the name of V-10, manufactured by the Special Foods Co., Redwing, Minn. It is prepared from a mixture of soy bean and special wheat flour and is very palatable, attractive in taste as well as highly nutritious. It contains 25.1% high-quality protein and without supplementation induces better growth in young rats than equivalent amounts of casein. It also contains 1.45μγ per gram of vitamin B_{12}.

because of serious complications of gastrointestinal hemorrhage or intercurrent infection. Included among these benefits are not only the control or disappearance of ascites but also improvement in nutritional status, reappearance of a sense of well-being, and a restoration toward normal of nitrogen balance and the usual battery of liver-function tests. It is common clinical experience that liberalization of the dietary restrictions becomes possible in many cases, as clinical progress develops, so that sodium intake may safely be increased up to 1 or 2 gm. daily, or even more.

Salt Restriction.—Since the diet represents the major source of salt intake, there is little else in this regard to require attention. It is obviously of importance to omit the use of drugs which contain sodium, such as sodium acetylsalicylate and sodium bicarbonate, and administration of parenteral fluid, when necessary, may be isotonic or hypertonic with glucose or fructose as 5% or 10% solution in water for injection U. S. P. The sodium content of drinking water is almost never of sufficient magnitude to present a practical problem. If a hyponatremic state has inadvertently been induced through the too vigorous employment of diet, diuretics, and paracentesis, the deliberate administration of isotonic or even hypertonic saline may at times become necessary for the management of a serious complication and to restore reactivity to diuretic agents. In fact, an impressive diuresis and natriuresis may be obtained at times in diuretic-fast patients through the administration of a repleting dose of several grams of sodium chloride.

Antibiotics.—Fever is a common phenomenon in cirrhosis, found by some observers to be present in 80% to 90% of patients. In a relatively small proportion of these patients it may be associated with the presence of a recognized intercurrent infection, but in the majority of patients its cause remains unknown, and it is often, if not usually, unaffected by the use of adequate antibiotic therapy. When the cause of fever can be identified, especially if the infecting microorganism can be isolated, antibiotic therapy may be effectively instituted, the choice of therapeutic agent depending upon specific sensitivity as determined by in vitro testing.

Mention should be made of the effect of chlortetracycline (Aureomycin), which, in experimental studies in animals, has been found to exert a protective action which delays the development of dietary hepatic necrosis.[47] The beneficial effect of this antibiotic, as well as that of several others, has been attributed to its growth-suppressing action on the normal intestinal flora. Clinical observations [48] have failed to reveal any striking therapeutic benefit in cirrhotic patients through the use of chlortetracycline, despite some equivocal evidence of effectiveness. Accurate evaluation of these agents is admittedly difficult in a disease as unpredictable and capricious as cirrhosis, but the evidence, up to the present time at least, is not convincing, and the administration of antibiotics, therefore, is not usually included in the program of treatment unless specific indications are found. I have had no experience in the routine use of chlortetracycline in this disease.

Paracentesis. — The presence of ascites, particularly when the volume of fluid is excessively large, not only is the cause of marked discomfort to the patient but also, by the mechanical effects of distention, interferes with appetite and, by compression of the iliac veins, produces obstruction to venous return of blood from the legs, with massive edema. Accordingly, removal of this fluid by paracentesis is a standard procedure both for subjective relief and for its true beneficial effect upon the course of the disease. Little or no difficulty is ordinarily experienced with the procedure, and drainage from the wound often continues for many days afterward. It should not be forgotten, however, that the paracentesis fluid contains large amounts of protein and electrolytes, so that a very substantial depletion of both may follow. It may justifiably be argued that these constituents of ascitic fluid are inert and metabolically inactive anyway, but the

repeated removal of such accumulations, especially if accompanied by a low-sodium and poor food intake, with repetitive use of electrolyte-depleting diuretics, may lead to serious metabolic complications. For this reason, electrolyte and protein balance must be kept constantly in mind.

Diuretics.—In a disease characterized by abnormal retention of both sodium and water, the therapeutic use of diuretics to force the excretion of both is natural and logical. The best of the available agents are the mercurials, such as meralluride (Mercuhydrin), mercurophylline (Mercuzanthin), mercaptomerin (Thiomerin), and mersalyl (Salyrgan). Their action is upon the renal tubule, without any appreciable effect upon glomerular filtration rate. Sodium and water excretion may be increased from 10- to 50-fold and 6- to 12-fold, respectively. For each 140 mEq. (3.2 gm.) of sodium lost, 1 liter of water must be excreted, and the urine volume in some patients may rise to 4 to 6 liters daily; in general, however, the diuresis induced in cirrhotic patients is usually less impressive than that seen in other edematous states. After acidification of the urine for one day with ammonium chloride, in a dose of 1 to 2 gm. four times daily, the mercurial diuretic is given by subcutaneous injection in a test dose of 0.5 cc. If no untoward reaction follows, indicative of idiosyncrasy to the drug, the full 2 cc. dose may be given on the following day and at approximately three-day intervals thereafter. I have usually used meralluride, but clinical studies indicate very little basis for preference among the presently available compounds. Special mention should be made of orally administered mercurial agents, the best of which is believed to be chlormerodrin (Neohydrin), a preparation four or five times more potent than the other drugs listed above, dispensed in tablet form, the dose of which is three to eight tablets daily.

One of the common obstacles to the successful use of mercurial diuretics is the development of a refractory state, characterized chemically by the changes of hypochloremic alkalosis, with a low plasma chloride, high bicarbonate, and a normal to mildly depressed sodium level. It is due to the disproportionately large renal excretion of the chloride ion induced by the therapeutic agent and is corrected by the administration of ammonium chloride. If the latter drug is continuously administered with the diuretic, according to common practice, this problem is much less likely to occur.

Complications.—Severe upper gastrointestinal hemorrhage from esophageal varices is the commonest serious complication of hepatic cirrhosis and is also the commonest cause of death. The immediate threat must be handled as an emergency situation by means of repeated transfusions of whole blood and the use of esophageal tamponade by means of a balloon-tipped tube, which may be introduced to the exact position necessary to bring counterpressure at the cardiac orifice and for several centimeters proximal to that point. Such a tube may be left in place for several days, during which time feeding obviously must be carried on parenterally. Specially designed tubes have been devised, however, to provide a rigid inner tube through which liquid feeding may be maintained. Adequate control of bleeding may be judged by close observation of pulse, blood pressure, and clinical evidences of shock. Simultaneous efforts should be directed to restoration of a normal or improved prothrombin content of blood, by means of parenterally administered vitamin K, and/or the transfusion of fresh whole blood. The latter measure, brief as its effect may be, is the only recourse when liver damage is so extreme that spontaneous production of prothrombin cannot occur. Immediate surgical intervention to stop bleeding has been advocated in the past, for the purpose of either ligating or sclerosing the dilated veins, but the operative mortality is very high, and, in my opinion, is usually not justified.

Hepatic coma must always be regarded as a near-terminal complication and usually ends fatally. Its appearance should indicate the probability of a very grave prognosis.

Therapeutic efforts to meet it consist of the intravenous infusion by constant slow drip of 10% glucose or fructose in water for injection U. S. P. supplemented with any good multivitamin preparation and the maintenance of protein nutrition as far as possible with a nutritious diet mixture, in a liquid form, if necessary, introduced by stomach tube if the patient is unconscious. Cortisone has been used by injection in large doses, of 250 mg. four times daily, but the benefits have been temporary only and very disappointing. Final evaluation of steroid therapy in this situation is difficult, and its effectiveness remains uncertain.

COMMENT

The successful therapeutic management of cirrhosis of the liver is best handled as a team project involving the internist, the dietitian, and the nursing staff, with occasional need for active surgical cooperation. In a chronic disease of this sort, with a spontaneously variable course, it is often difficult to assess the precise value of various measures. Enormous patience is required on the part of the entire attending staff, since satisfactory food intake, the most important single item in the plan of management, will often be disappointing for long periods of time, and cooperation by the patient may be very poor. Plans must be made for the treatment to be as chronic as the disease, and a long period of hospitalization may serve not only as a turning point in a previously downward course but also as a period of reeducation into a new pattern of living, during which proper food habits may be well established and the first stages in reducing or eliminating alcoholic intake can be attempted. Rehabilitation of cirrhotic patients, therefore, extends far beyond the actual dietary details and remedial medications employed. For the pathway back to health for these persons is a long, rough, and discouraging one, especially when alcoholism is a major etiological factor, and necessarily involves the acceptance of a diet which is of low palatability for many persons combined with abstinence from alcohol. It is for these reasons that an attitude of patience and sympathetic understanding on the part of the physician and his associates is important enough to justify special comment.

Of the voluminous literature in this field, I would like to cite especially the papers by Patek, Post, Ratnoff, Mankin, and Hillman [49]; by Chalmers and Davidson,[50] and by Davidson.[51]

REFERENCES

1. Klatskin, G.: The Role of Alcohol in the Pathogenesis of Cirrhosis, Yale J. Biol. & Med. **26**:23, 1953.

2. Patek, A. J., Jr.: Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, Proc. Soc. Exper. Biol. & Med. **37**:329, 1937.

3. Patek, A. J., Jr.: Treatment of Cirrhosis of the Liver by Nutritious Diet and Supplements Rich in Vitamin B Complex, J. Clin. Invest. **20**:481, 1941.

4. Strauss, M. B.: Alcoholic Polyneuritis, Am. J. M. Sc. **189**:378, 1935.

5. Spies, T. D., and DeWolf, H. F.: Observations on the Etiological Relationship of Severe Alcoholism to Pellagra, Am. J. M. Sc. **186**:521, 1933.

6. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, Tr. A. Am. Physicians **51**:341, 1936.

7. Weiss, S.: Occidental Beriberi with Cardiovascular Manifestations, J. A. M. A. **115**:832, 1940.

8. Connor, C. L.: Fatty Infiltration of the Liver and the Development of Cirrhosis in Diabetes and Chronic Alcoholism, Am. J. Path. **14**:347, 1938.

9. Connor, C. L.: The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver, J. A. M. A. **112**:387, 1939.

10. Best, C. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, J. Physiol. **79**:94, 1933.

11. Gyorgy, P., and Goldblatt, H.: Hepatic Injury on a Nutritional Basis in Rats, J. Exper. Med. **70**:185, 1939.

12. Russakoff, A. H., and Blumberg, H.: Choline as an Adjuvant to the Dietary Therapy of Clinical Cirrhosis of the Liver, Ann. Int. Med. **21**:848, 1944.

13. Tucker, H. F., and Eckstein, H. C.: The Effect of Supplementary Methionine and Cystine on the Production of Fatty Livers by Diet, J. Biol. Chem. **121**:479, 1937.

14. Gyorgy, P.: Experimental Hepatic Injury, Am. J. Clin. Path. **14**:67, 1944.

15. Eddy, J. H.: Methionine in the Treatment of Toxic Hepatitis, Am. J. M. Sc. **210**:374, 1945.

16. Wade, L. J.: Recent Advances in the Therapy of Cirrhosis of the Liver, M. Clin. North America **29**:479, 1945.

17. Du Vigneaud, V.; Simmonds, S.; Chandler, J. P., and Cohn, M.: Synthesis of Labile Methyl Groups in the White Rat, J. Biol. Chem. **159**:755, 1945.

18. Arnstein, H. R. V., and Neuberger, A.: The Effect of Cobalamine on the Quantitative Utilization of Serine, Glycine and Formate for the Synthesis of Choline and Methyl Groups of Methionine, Biochem. J. **55**:259, 1953.

19. Labby, D. H.; Shank, R. E.; Kunkel, H. G., and Hoagland, C. L.: Intravenous Therapy of Cirrhosis of the Liver, J. A. M. A. **133**:1181, 1947.

20. Gilbert, A., and Lereboullet, P.: Des Urines retardées (opsiurie) dans les cirrhoses, Compt. rend. Soc. biol. **3**:276, 1901.

21. Ratnoff, O. D., and Patek, A. S., Jr.: The Natural History of Laennec's Cirrhosis of the Liver: An Analysis of 386 Cases, Medicine **21**:207, 1942.

22. Adlersberg, D., and Fox, C. L., Jr.: Changes in the Water Tolerance Test in Hepatic Disease, Ann. Int. Med. **19**:642, 1943.

23. Jones, C. M., and Eaton, F. B.: The Prognostic Significance of a Spontaneous Diuresis in Acute or Subacute Disease of the Liver, New England J. Med. **213**:907, 1935.

24. Ralli, E. P.; Robson, J. S.; Clarke, D., and Hoagland, C. L.: Factors Influencing Ascites in Patients with Cirrhosis of the Liver, J. Clin. Invest. **24**:316, 1945.

25. Farnsworth, E. B.: Electrolyte Partition in Patients with Edema of Various Origins, Am. J. Med. **4**:338, 1948.

26. Eisenmenger, W. J.; Ahrens, E. H., Jr.; Blondheim, S. H., and Kunkel, H. G.: The Effect of Rigid Sodium Restriction in Patients with Cirrhosis of the Liver and Ascites, J. Lab. & Clin. Med. **34**:1029, 1949.

27. Gabuzda, G. J., Jr.; Treager, H. S., and Davidson, C. S.: Hepatic Cirrhosis: Factors Contributing to the Failure to Excrete Urinary Sodium During the Accumulation of Ascites and Edema, J. Clin. Invest. **29**:814, 1950.

28. Goodyer, A. V. N.; Relman, A. S.; Lawrason, F. D., and Epstein, F. H.: Salt Retention in Cirrhosis of the Liver, J. Clin. Invest. **29**:973, 1950.

29. Chart, J. J., and Shipley, E. S.: The Mechanism of Sodium Retention in Cirrhosis of the Liver, J. Clin. Invest. **32**:560, 1953.

30. Bongiovanni, A. M., and Eisenmenger, W. J.: Adrenal Cortical Metabolism in Chronic Liver Disease, J. Clin. Endocrinol. **11**:152, 1951.

31. Leutscher, J. A., Jr., and Johnson, B. B.: Observations on the Sodium-Retaining Corticoid in the Urine of Children and Adults in Relation to Sodium Balance and Edema, J. Clin. Invest. **33**: 1441, 1954.

32. Chart, J. J.; Gordon, E. S.; LeSher, M., and Helmer, P.: Liver Inactivation of Sodium Retaining Hormone, J. Clin. Invest., to be published.

33. Harris, J. F.; Lloyd, C. W., and Lobotsky, J.: Some Studies of Posterior Pituitary and Adrenal Cortical Interrelationships in Patients With and Without Cirrhosis of the Liver, J. Clin. Invest. **32**:885, 1953.

34. Eisenmenger, W. J.; Blondheim, S. H.; Bongiovanni, A. M., and Kunkel, H. G.: Electrolyte Studies on Patients with Cirrhosis of the Liver, J. Clin. Invest. **29**:1491, 1950.

35. Combined Staff Clinic: Mechanisms of Ascites Formation, Am. J. Med. **9**:102, 1950.

36. Thorn, G. W.; Armstrong, S. H., Jr., and Davenport, V. D.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation: XXXI. The Use of Salt Poor Concentrated Human Serum Albumin Solution in the Treatment of Hepatic Cirrhosis, J. Clin. Invest. **25**:304, 1946.

37. Faloon, W. W.; Eckhardt, R. D.; Cooper, A. M., and Davidson, C. S.: The Effect of Human Serum Albumin, Mercurial Diuretics and a Low Sodium Diet on Sodium Excretion in Patients with Cirrhosis of the Liver, J. Clin. Invest. **28**:595, 1949.

38. Prentice, T. C.; Siri, W., and Joiner, E. E.: Quantitative Studies of Ascitic Fluid Circulation with Tritium Labelled Water, Am. J. Med. **13**:668, 1952.

39. Hilton, J. G.: Effects of Mercurial Diuresis in Patients with Ascites Due to Cirrhosis, Am. J. Med. **12**:311, 1952.

40. Blakemore, A. H.: Indications for Portacaval Anastomosis: Analysis of Cases, Surg. Gynec. & Obst. **84**:645, 1947.

41. Linton, R. R.: Portocaval Shunts in Treatment of Portal Hypertension with Special Reference to Patients Previously Operated upon, New England J. Med. **238**:723, 1948.

42. Rousselot, L. M.: The Present Status of Surgery for Portal Hypertension, Am. J. Med. **16**: 874, 1954.

43. Adams, R. D., and Foley, J. M.: The Neurological Disorder Associated with Liver Disease, A. Res. Nerv. & Ment. Dis., Proc. **32**:198-237, 1953.

44. Snell, A. M., and Butt, H. R.: Hepatic Coma: Observations Bearing on Its Nature and Treatment, Tr. A. Am. Physicians **56**:751, 1952.

45. Traeger, H. S.; Gabuzda, G. J.; Ballore, A. N., and Davidson, C. S.: Blood "Ammonia" Concentration in Liver Disease and Liver Coma, Metabolism **3**:99, 1954.

46. Schwartz, R.; Phillips, G. B.; Gabuzda, G. J., and Davidson, C. S.: Blood Ammonia and Electrolytes in Hepatic Coma, J. Lab. & Clin. Med. **42**:499, 1953.

47. Gyorgy, P.: Vitamin B_{12}, Folic Acid, and the Lipotropic Agents, in Liver Injury: Transactions of the Ninth Conference, April 27 and 28, 1950, edited by F. W. Hoffbauer, New York, Josiah Macy, Jr. Foundation Publications, 1951.

48. Shaffer, J. M.; Bluemle, L. W.; Sborov, V. M., and Neefe, J. R.: Studies on the Use of Aureomycin in Hepatic Disease: Aureomycin Therapy in Chronic Liver Disease, Am. J. M. Sc. **220**:173, 1950.

49. Patek, A. J., Jr.; Post, J.; Ratnoff, O. D.; Mankin, H., and Hillman, R. W.: Dietary Treatment of Cirrhosis of the Liver: Results in 124 Patients Observed During a 10-Year Period, J. A. M. A. **138**:543, 1948.

50. Chalmers, T. C., and Davidson, C. S.: A Survey of Recent Therapeutic Measures in Cirrhosis of the Liver, New England J. Med. **240**:449, 1949.

51. Davidson, C. S.: Cirrhosis of the Liver Treated with Prolonged Sodium Restrictions, J. A. M. A. **159**:1257, 1955.

Low-Sodium Diets

52. Dining Fine Without Brine, Milwaukee Dietetic Association and Wisconsin Heart Association, 642 N. Fifth St., Milwaukee 3, 1952.

53. Hasker, R. R.: The Cook Book for Low Sodium Diets, The Massachusetts Heart Association, Inc., 500 Commonwealth Ave., Boston, 1950.

54. Payne, A. S., and Calahan, D.: The Low Sodium Cook Book, Little, Brown & Company, Boston, 1953.

55. Planning Low Sodium Meals, Newton Health Department, Newton, Mass., 1951.

Case Reports

POSTERIOR INFERIOR CEREBELLAR ARTERY SYNDROME OF WALLENBERG AFTER CHIROPRACTIC MANIPULATION

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IT HAS been known for some time that chiropractic manipulation of the vertebral column can cause damage to the encased spinal cord and its roots. For instance, injury to the cauda equina from a nucleus pulposus traumatically herniated by manipulation has been described.[1] Paraplegia may prove to be a more serious sequel to these manipulative procedures.* Even more complicated and serious neurologic results may occur with dislocation of the atlas on the axis as a result of chiropractic manipulation of the neck and head.[4]

While such dangers to the spinal cord and spinal roots would seem to be readily understandable, the involvement of neural structures in the posterior fossa of the skull might seem more remote. Yet damage to the cerebellum and brain stem have resulted from chiropractic manipulation.† Damage to such structures can be quickly fatal or may leave unfortunate neural deficits. We have had the opportunity to study a young woman who developed the classical Wallenberg syndrome following chiropractic manipulation of her head and neck but who made an uneventful recovery with few residua. It was felt that a report of this case might help to emphasize the importance of this intracranial complication following chiropractic manipulation.

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From the Department of Neurology, School of Medicine, University of Pennsylvania (Dr. Schwarz).

* References 2 and 3.

† References 3 and 5.

REPORT OF CASE

On Nov. 4, 1954, a 28-year-old white woman visited a chiropractor to get treatment for a "head cold." Immediately after the manipulation of her neck, she sat up, felt "dizzy," and noticed that the right side of her face and her left extremities were "numb." She felt generally weak. She could not walk without support and had to be taken home by her sister and brother-in-law. It was noticed then that the right side of her face "looked different." The following day, she remained in bed and that evening complained of some pain in the back of her head on the right side. She became nauseated, "dizzy," and "weak all over" and fainted.

The patient complained of blurring of vision in her right eye. She had nausea followed by vomiting on several occasions. Although she said she felt weak, she was able to walk by holding on to nearby objects.

She had trouble swallowing solid foods. Liquids would come out of her nose unless she sipped them slowly. Her speech was somewhat nasal and slurred. She never had any trouble in chewing. There was no history of tinnitus, no difficulty in hearing, no diplopia, and no trouble in smelling or tasting. She never had a fever.

A neurologic examination was performed by one of us (G. A. S.) on Nov. 28, 1954, and showed the following results: The borders of the right optic nerve head were somewhat hazy, and the retinal veins seemed full. However, there was no true papilledema. The left optic nerve head showed no changes. The visual fields were full as tested by gross confrontation. The right pupil was smaller than the left. The pupils reacted well to light and in accommodation-convergence. There were a few unsustained nystagmoid jerks on right lateral gaze. The muscles of the face, tongue, and jaws moved fully. The soft palate deviated to the left on phonation. The patient spoke clearly and well, although there was a nasal quality to her speech. The nasal and corneal reflexes were diminished on the right. The other cranial nerves were intact.

The patient's gait was unsteady. She preferred to hold on to someone when walking, although she could walk alone. In the Romberg position, with her eyes open or closed, she tended to sway a bit to the right.

There was no demonstrable dysmetria, dyssynergia, or dysdiadokokinesia.

There was no disturbance in muscle power, tone, or volume.

Touch, pin-prick, and temperature sensation were impaired on the right side of her face. Touch perception was impaired a little bit in her left foot and the distal portion of her left leg. The senses of pain and temperature were markedly impaired in her left upper and lower extremities and in the left side of her body. Vibration sense and position sense were intact throughout.

The tendon and periosteal reflexes and the abdominal reflexes were all present and equally active. There were no pathologic reflexes.

On Nov. 30, 1954, the patient was admitted to the Hospital of the University of Pennsylvania. The laboratory studies showed 91% (13.7 gm. per 100 ml. of blood) of hemoglobin and 4,500,000 red blood cells per cubic millimeter of blood, of which 64% were polymorphonuclear cells, 34% were lymphocytes, and 2% were monocytes. The blood urea nitrogen was 11 mg/100 cc., and the fasting blood sugar was 93 mg/100 cc. Urinalysis showed nothing abnormal. Her blood Kolmer and Kline tests were nonreactive. The cerebrospinal fluid was under normal pressure and contained 26 mg/100 cc. of protein.

The roentgenogram of her skull showed some prominence of the digital markings. The bones of the sella turcica showed no erosion. The calcified body was not displaced. Special studies of the occipitoatlantoaxial articulations and odontoid process disclosed nothing abnormal.

Her visual fields were full as tested by the perimeter and the tangent screen. The ophthalmologist also observed diminished corneal sensitivity and a smaller pupil on the right side.

On Feb. 8, 1955, the patient stated that her gait was less unsteady. She could use her left hand much better than before. She no longer dropped objects from this hand. She now noted a pins-and-needles feeling in her left foot.

The neurologic examination on this date showed her gait to be much less ataxic. Actually, she could walk very well without support. The Romberg test showed no swaying. Check was impaired in her right upper extremity. There was a slight dysmetria on doing the finger-to-nose test on the right. Her right pupil was almost as large as the left. There was a slight unsustained rotatory nystagmus on right lateral gaze. Her soft palate pulled up and to the left. The palatal reflex seemed to be absent on the right side. The corneal and nasal reflexes were impaired on the right side. Touch was impaired on her right forehead. Pain and temperature were impaired in the right face, left upper extremity, left lower chest, abdomen, and left lower extremity. Her muscle status was intact. Her reflexes were not abnormal.

COMMENT

In reviewing the literature, we discovered that three cases had been previously reported in which brain stem injury had followed chiropractic manipulation. In 1947, Pratt-Thomas and Berger [3] described the case of a 32-year-old man who went to a chiropractor for "adjustments" for his headaches and "giddy" feelings. During his last manipulation, the patient lost consciousness. When he revived, it was evident that he had medullary damage. He was sent to a hospital but died 48 hours later. An autopsy showed a thrombosis of his basilar artery, his left anterior inferior cerebellar artery, and his right posterior inferior cerebellar artery. These authors also described a 35-year-old woman who had been periodically visiting a chiropractor for "hay fever." After a manipulation of her head and neck she became "dizzy." The following day she was sent to the hospital in an unconscious state and died after a few hours. An autopsy revealed a thrombosis of the basilar artery, the right vertebral artery, and the left posterior inferior cerebellar artery.

Then, in 1953, Kunkle, Muller, and Odom [5] described a 35-year-old man who had been receiving a series of neck manipulations by a chiropractor for headache. The last manipulation was unusually vigorous, involving stretching and rotary neck movements, along with firm pressure on the right side of the neck. He developed sudden neurologic symptoms felt to be due to an insufficiency of his right posterior inferior cerebellar artery. A year later, he presented a residual ataxic gait, nystagmus, numbness and dryness of the right side of the face, slight numbness of the left side of the face, and blurring of vision.

While stretching, tearing, or compression of the parenchyma directly will explain spinal cord or spinal root damage following chiropractic manipulation, the brain stem and cerebellum cannot be so involved. Damage to these latter structures must be by interference with their blood supply. Much thought has been given to the mechanism by which such vascular damage can occur. Kunkle and

co-workers [5] felt that the vertebral arteries were particularly vulnerable to injury by such manipulations in that portion of these vessels which stretches from the atlas into the skull. They felt that the atlanto-occipital portions of the vertebral arteries are of necessity very flexible in order to meet the wide mobility of the occipitoatlantal and atlantoaxial joints. They referred to the interesting tests of de Kleyn and Nieuwenhuyse,[6] who demonstrated in cadavers that the circulation through one vertebral artery could be impaired seriously if the head were overextended and tilted to the opposite side. Kunkle and coworkers [5] and de Kleyn and Nieuwenhuyse [6] also stressed the fact that variations in the size and position of the vertebral arteries could occur and that persons with such vascular variations would undoubtedly be readily susceptible to unusual stresses of this circulation. Lindenberg [7] has recently stressed the ready compressibility of the posterior inferior cerebellar artery at points where it is closest to the posterior rim of the foramen magnum. Such factors as these would seem to us to offer a reasonable explanation of the vascular syndrome which occurred in our young patient.

Occlusion of the posterior inferior cerebellar artery or one of its branches is the "most common vascular lesion of the brain stem.[8]" The commonest etiologic basis for the Wallenberg syndrome is said to be hypertension and/or atherosclerosis.[9] It would seem to us that when this syndrome is found in a young person with no other vascular disease a traumatic cause should be sought.

The fact that thromboses were found pathologically in the two autopsied cases may be important in the light of the recent successful use of anticoagulants in intermittent insufficiency of the basilar artery.[10] It is suggested that, in the future, if such brain stem syndromes follow chiropractic head and neck manipulation prompt anticoagulant therapy may well be life-saving.

SUMMARY

A case of Wallenberg's syndrome in a young girl is reported. It followed immediately upon chiropractic manipulation of the head and neck, Recovery was almost complete.

The mechanism of the production of such a disorder is discussed. Early diagnosis would seem essential because of the benefits that might be obtained from prompt anticoagulant therapy.

REFERENCES

1. Fischer, E. D.: Ruptured Intervertebral Disc Following Chiropractic Manipulation: Case, Kentucky M. J. **41**:14, 1943.

2. Lièvre, J. A.: Paraplégie due aux manoeuvres d'un chiropractor, Rev. rhumat. **20**:708, 1953.

3. Pratt-Thomas, H. R., and Berger, K. E.: Cerebellar and Spinal Injuries After Chiropractic Manipulation, J. A. M. A. **133**:600, 1947.

4. Blaine, E. S.: Manipulative (Chiropractic) Dislocation of the Atlas, J. A. M. A. **85**:1356, 1925.

5. Kunkle, E. C.; Muller, J. C., and Odom, G. L.: Traumatic Brain-Stem Thrombosis: Report of a Case and Analysis of the Mechanism of Injury, Ann. Int. Med. **36**:1329, 1952.

6. de Kleyn, A., and Nieuwenhuyse, P.: Schwindelanfälle and Nystagmus bei einer bestimmten Stellung des Kopfes, Acta oto-laryng. **11**:155, 1927.

7. Lindenberg, R.: Compression of Brain Arteries as Pathogenetic Factor for Tissue Necroses and Their Areas of Predilection, J. Neuropath. & Exper. Neurol. **14**:223, 1955.

8. Merritt, H. H.: Textbook of Neurology, Philadelphia, Lea & Febiger, 1955, p. 187.

9. Riley, W. H.: The Syndrome of Occlusion of the Posterior Inferior Cerebellar Artery, Bull. Battle Creek Sanitarium & Hosp. Clin. **25**:1, 1930.

10. Millikan, C. H.; Siekert, R. G., and Shick, R. M.: Studies in Cerebrovascular Disease: III. The Use of Anticoagulant Drugs in the Treatment of Insufficiency or Thrombosis Within the Basilar Arterial System, Proc. Staff Meet. Mayo Clin. **30**:116-126, 1955.

IDIOPATHIC CLUBBING AND HYPERTROPHIC OSTEOARTHROPATHY

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WHEN CLUBBED fingers are noted in the course of a physical examination, the clinician considers the possibility of an underlying chronic disease, particularly cardiac or pulmonary. The following case is deemed worthy of presentation because it illustrates clubbing of the digits and the bone changes of hypertrophic osteoarthropathy in a healthy young man without recognizable disease, in whom cardiac catheterization studies revealed normal cardiopulmonary physiology.

REPORT OF CASE

A 23-year-old white man was found to have symmetrical clubbing of the fingers and toes in the course of a routine college entrance physical examination in September, 1953. Prior to this he had been unaware of any abnormality. The past history included occasional upper respiratory infections, scarlet fever as a child, and a mild pneumonic episode in 1947. He denied cyanosis. The history was negative for congenital heart disease or for any serious illness. His good health became more apparent when questioning revealed that he had been on his high school track team, was able to run a mile without difficulty, and had enrolled in college intending to major in physical education.

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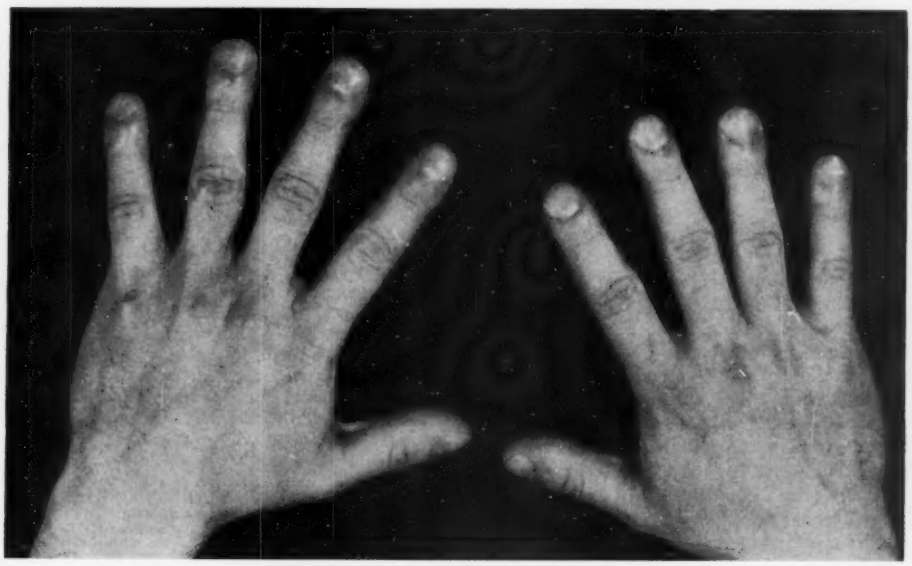
The family history was negative for clubbing, but other members of the family were unavailable for examination. It seemed probable that the history was correct, since the patient was questioned repeatedly after his attention had been called to the appearance of clubbed digits and he had visited his family at home.

Physical examination was normal with the exception of symmetrical clubbing of the fingers and toes (Fig. 1). The photograph reveals the clubbing, which was, however, even more apparent clinically, as noted by numerous observers. Pyke [1] has described the findings necessary for diagnosis, the essential change being obliteration of the angle between nail and nail bed, and this change was ap-

Fig. 1.—Symmetrical clubbing of the fingers.



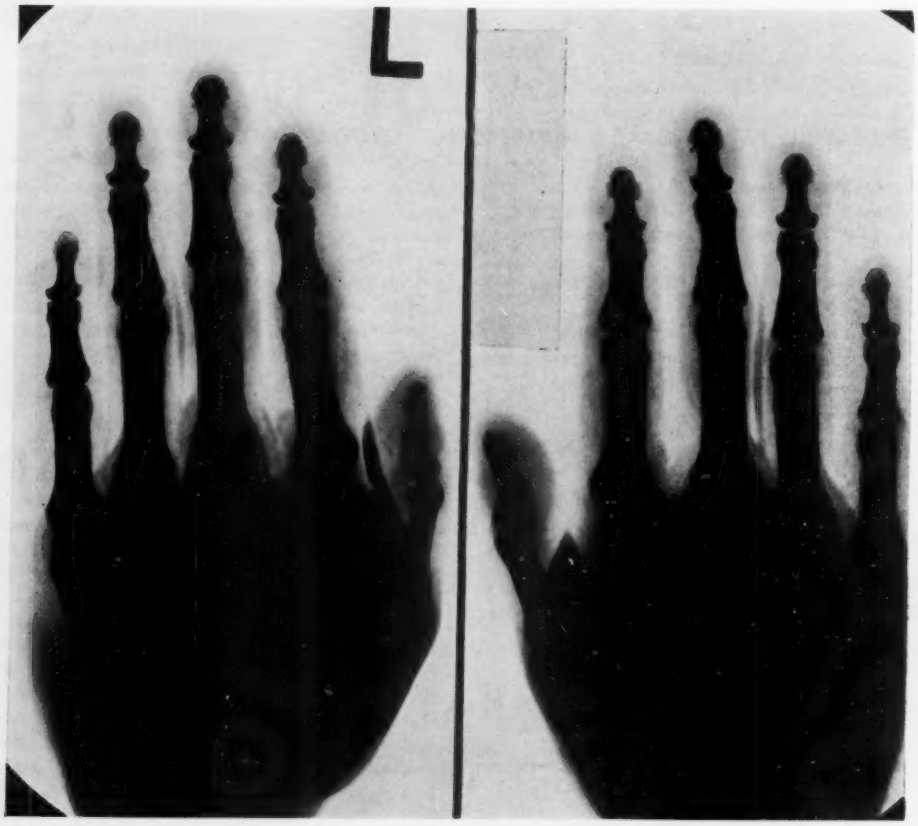


Fig. 2.—Roentgenogram of fingers, showing broadening of tufts of terminal phalanges and serration, particularly in phalanges 2, 3, and 5.

parent in our patient. The lung fields were clear; the heart sounds were distinct and of good quality. The liver and spleen were not palpable. Hair distribution was normal. The ears and lips were not cyanotic. The clubbed nail beds presented a very questionable cyanotic tinge.

Teleoroentgenogram and cardiac fluoroscopy were normal. The electrocardiogram was within normal limits. Roentgenograms of the tibae were normal; those of the hands and feet revealed the burr-like proliferative changes of the ungual phalanges described by Craig[2] (Fig. 2). This patient, then, had not only soft tissue changes but also the early bone changes of hypertrophic osteoarthropathy. Upper gastrointestinal roentgenograms were normal. Other laboratory data were normal and are summarized in Table 1. Skin temperatures taken at the finger tips with the electric thermocouple were between 31.5 and 32 C (88.4 and 89.6 F).

At this point of investigation it was thought that a small septal defect might exist, and the patient was referred to the cardiovascular section of the

TABLE 1.—*Summary of Laboratory Tests*

Hemoglobin	15.6 gm./100 ml. blood
Mean corpuscular hemoglobin	30γ
Red blood corpuscles	5,200,000 million/cu. mm. blood
White blood corpuscles	6,450/cu. mm. blood
Differential count	N, 49%; juvenile N, 8%; L, 40%; M, 3%
Sedimentation rate	1 mm. in an hour (Wintrobe-Landsberg)
C-reactive protein	Negative
Total protein	7.4 gm./100 ml. serum
Serum albumin	5.25 gm./100 ml. serum
Serum globulin	2.15 gm./100 ml. serum
Albumin/globulin ratio	2.44:1
Alkaline phosphatase	1.7 Bodansky units
Serum phosphorus	3.8 mg./100 mm. serum
Thymol turbidity	1 unit
Thymol flocculation	Negative
Cephalin cholesterol flocculation	1+ in 24 and 48 hours
Urine	Clear; specific gravity, 1.016; 0 sugar and albumin; 0 WBC, RBC, and casts

Department of Medicine at Marquette University for consideration of cardiac catheterization. Preliminary studies at the clinic included a phonocardiogram, which failed to disclose cardiac murmurs. Venous catheterization was performed, and arterial oxygen samples were obtained by means of a Cournand cannula in the right brachial artery. Table 2 lists the results, all of which were within normal limits. The patient has been seen periodically since 1953, and no evidence of ill health has occurred.

TABLE 2.—*Venous Catheterization and Oxygen Saturation Studies*

	Values	Mm. Hg Blood Pressure,
Blood O_2 content, cc./L.		
Superior vena cava	133.5	....
Inferior vena cava	155.6	....
Right atrium	151.5	4
Right ventricle	154.7	18/2
Main pulmonary artery		
At rest	157.1	42/8
After exercise	105.5	....
Right brachial artery		
At rest	210.8	....
After exercise	213.2	....
After 100% O_2 for 3 min.	221.8	....
Oxygen consumption, cc./min.		
Rest	231	....
Exercise	1,335	....
Cardiac output, L./min.		
Rest	4.12	....
Exercise	12.4	....
Oxygen capacity, cc.	235.5	....
O_2 saturation, %		
Room air	90	....
With 100% O_2	94	....
Pulmonary function		
Inspiratory reserve, cc.	2,484	....
Expiratory reserve, cc.	1,283	....
Tidal air, cc.	786.6	....
Vital capacity, cc.	4,057	....
Maximum breathing capacity, L./min. (normal, 82-169)	94.5	....

COMMENT

Reports * of clubbing occurring secondary to some primary disease are numerous. Mendlowitz [8] grouped such cases under the designation of acquired clubbing. Less emphasized is the hereditary group, in which a family history can be obtained, and the idiopathic group, in which a family history is not apparent. The case reported here appears to fall into the last category and represents to the best of our knowledge the first reported case in which cardiac catheterization studies have been obtained to rule out occult cardiac or pulmonary disease. Recent articles tend to stress the benign aspect of idiopathic clubbing.† The present case adds to this concept.

A final point is the possibility that what we have called an idiopathic disease is in fact secondary to a primary disease which eludes diagnosis. Keats and Bagnall [11] and Berk [12] mention that clubbing and its more advanced stage of osteoarthropathy may be the initial finding in pulmonary neoplasm. Craig [2] reported four cases in which osteoarthropathy preceded pulmonary symptoms by 8 to 11 months, and in the Case Record of the Massachusetts General Hospital [7] is reported one in which pulmonary symptoms did not appear for one and one-half years. The probability of acquired disease in our case seems quite unlikely for several reasons. The young age, the continuation of good health after an observation period of two years, and the intensive studies he has had all militate against this possibility.

SUMMARY

A case of idiopathic clubbing with early hypertrophic osteoarthropathy is presented. The patient had always considered himself in good health, and the abnormality was discovered during a routine physical examination. This report is believed to be the first which includes venous catheterization and brachial artery oxygen saturation studies, these studies being done to exclude cardiac septal defect and pulmonary disease. Our case adds to those already in the literature which build a concept of simple clubbing and osteoarthropathy as manifestations of a disease of unknown cause, with a favorable prognosis.

Marquette University School of Medicine gave permission to use the data obtained by cardiac catheterization.

REFERENCES

1. Pyke, D. A.: Finger Clubbing: Validity as a Physical Sign, Lancet **2**:352-354 (Aug. 21) 1954.

2. Craig, J. W.: Hypertrophic Pulmonary Osteoarthropathy as the First Symptom of Pulmonary Neoplasm, Brit. M. J. **1**:750-752 (April 10) 1937.

* References 2-7.

† References 9-12.

3. Warthin, T. A.; Cooper, J. F., and Caputi, A. P.: Clubbing of Digits, Metaplasia of Urinary Bladder and Mucous Diarrhea, Arch. Int. Med. **86**:10-21 (July) 1950.

4. Fried, B. M.: Chronic Pulmonary Osteoarthropathy: Dyspituitarism as a Probable Cause, Arch. Int. Med. **72**:565-580 (Nov.) 1943.

5. Bloom, W.: Pituitary Implications in Hypertrophic Pulmonary Osteoarthropathy, Ann. Int. Med. **29**:361-370 (Aug.) 1948.

6. Pattison, J. D., Jr.; Beck, E., and Miller, W. B.: Hypertrophic Osteoarthropathy in Carcinoma of Lung, J. A. M. A. **146**:783-787 (June 30) 1951.

7. Case Records of the Massachusetts General Hospital: Case 31281, New England J. Med. **233**: 44-48 (July 12) 1945.

8. Mendlowitz, M.: Clubbing and Hypertrophic Osteoarthropathy, Medicine **21**:269-306 (Sept.) 1942.

9. Talbott, J. H., and Montgomery, W. R., Jr.: Familial Clubbing of Fingers and Toes, A. M. A. Arch. Int. Med. **92**:697-700 (Nov.) 1953.

10. Logue, J. T.: Osteoarthropathy and Simple Clubbing, U. S. Armed Forces M. J. **4**:1627-1631 (Nov.) 1953.

11. Keats, T. E., and Bagnall, W. S.: Chronic Idiopathic Osteoarthropathy, Radiology **62**:841-844 (June) 1954.

12. Berk, M.: Chronic Idiopathic Hypertrophic Osteoarthropathy, New England J. Med. **247**:123-126 (July 24) 1952.

Scientific Exhibits

RECENT METHODS IN THE STUDY AND TREATMENT OF ATHEROSCLEROSIS IN NORMAL SUBJECTS EIGHTY TO ONE HUNDRED YEARS OF AGE

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FOR THE past five years we have been engaged in an intensive study of lipid metabolism. The data in this series were derived from studying 500 subjects aged 13 to 100 years, in an attempt to determine which laboratory and clinical criteria are definitive in diagnosing atherosclerosis and which means are useful in its management. X-ray films of 1000 persons aged 50 to 100 years, including 335 patients 80 to 100 years of age, were reviewed. In this series were 100 normal subjects 80 to 100 years old in whom detailed lipid metabolic studies were made. These elderly persons, who were institutionalized for custodial care, had no previous history of coronary, metabolic, endocrine, or venereal disease and were considered to be "normal."

METHODS OF STUDY

Blood chemistry examinations were performed for creatinine, nonprotein nitrogen, and serum lipid partitions such as total cholesterol, phospholipid, neutral fats, and total lipids. Serum lipoprotein molecules (S_f 0-12 and S_f 12-400) were determined by the high-speed ultracentrifuge apparatus. The significance of the atherogenic potentialities from the S_f lipoprotein molecule values as indicated by the atherogenic index was utilized. Alpha- and beta-globulin fractions were obtained by paper electrophoresis to compare and correlate with the S_f molecule values. Ballistocardiograms and electrocardiograms were taken.

Roentgenograms of the thoracic and abdominal aortas were studied. Newer measurement concepts in the determination of aortic dilatation and new interpretations of the amount of calcification within the aorta were obtained. Ophthalmoscopic examinations for a more revealing eye ground classification of arteriosclerosis were done at periodic intervals. Gross and microscopic examinations of the aortas were performed in a scrupulous manner in all of the patients who died, and some new concepts were revealed. This exhibit presents, correlates, and compares the results of similar studies in younger subjects (25 to 80 years).

Our studies have shown that total lipids, certain serum lipoprotein molecules, atherogenic index, degree of aortic calcification, and degree of aortic dilatation all increase from youth until the age group of 60 to 75 years, after which there is a decline or reversal of biochemical and/or physical processes. We have termed this the "threshold age."

Current treatment of atherosclerosis in normal geriatric persons is discussed, especially what the physician should "do" and "not do." The following clinical topics are mentioned: type of diet; clinical value of lipotropic agents; recent antihypertensive drug combinations to lower elevated blood pressures (an abnormal finding); indiscriminate local usage of antibiotics for eye diseases; hormones for

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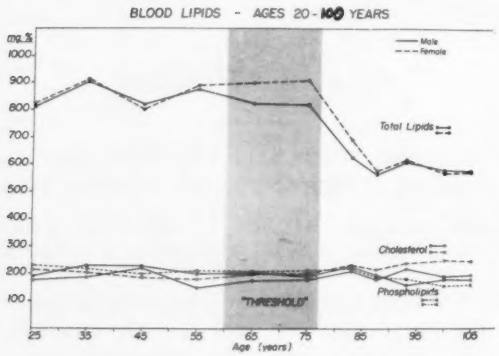

Fig. 1.—Serum total lipids, total cholesterol, and phospholipids.

osseous pain; drugs for senile agitation, tremor, and spasticity; instructions to prevent accidents, and the value of rehabilitation. The findings and results are presented by illustrated legends.

RESULTS

The Laboratory: New Methods, New Apparatus, New Concepts

Blood Chemistry Studies.—Creatinine and nonprotein nitrogen values show no significant variations in any age group. C^{14}-labeled cholesterol studies are inconclusive to date concerning factors involved in formation of atheromatous lesions.

There are no characteristic abnormalities of the blood cell counts in healthy persons over the age of 60. There is a tendency for the older person to show a slight average decrease in the red blood cell count and percentage of hemoglobin. However, this is not below the minimal normal for younger persons.

Cholesterol values, except for an insignificant rise in the group of older women, show no significant variations in any age group. Phospholipid values show no variation. Total lipids decrease significantly after the "threshold" age group (60 to 75 years). There is no difference between the male and female groups. High cholesterol values do not imply gross existing atherosclerosis (Fig. 1).

Abnormal ratios of phospholipids to cholesterol may occur when one component is altered disproportionately in comparison with the other component. One cannot assume that atherogenesis is more pronounced in the aged because of a phospholipid-cholesterol (P/C) ratio below 1.00, compared with 1.10 in the younger person. The P/C ratio is not constant, and ratios below 1.00 cannot always be considered suggestive of overt vascular disturbance or as an index of atherogenesis (Fig. 2).

Ultracentrifuge Techniques: Lipoprotein Molecules and Atherogenic Index.—By utilizing a highly specialized self-contained ultracentrifuge apparatus, it is possible to record, automatically, at repeated intervals, the particle size or molecular weight (by virtue of refractive gradients) of serum lipoproteins. The so-called standard classes of serum lipoproteins are the S_f 0-12 and the S_f 12-400. These classes were found to be elevated in groups with frank coronary disease. It has been maintained that until the age of 60 years the elevation of these classes is in agreement with the finding "that severe atherosclerosis does not inevitably accompany chronological aging." Hence, after many years, we have at our disposal a method for the possible prognostication and diagnosis of atherosclerosis (Fig. 3).

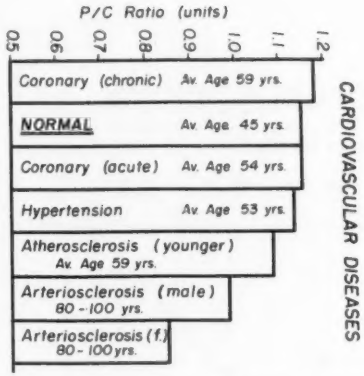

Fig. 2.—Significance of phospholipid-cholesterol (P/C) ratio.

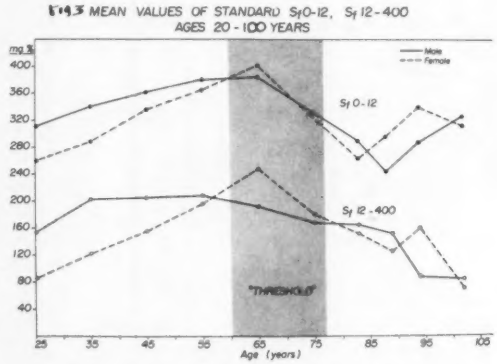

Fig. 3.—Standard S_f 0-12 and S_f 12-400 lipoproteins in subjects aged 20 to 100 years.

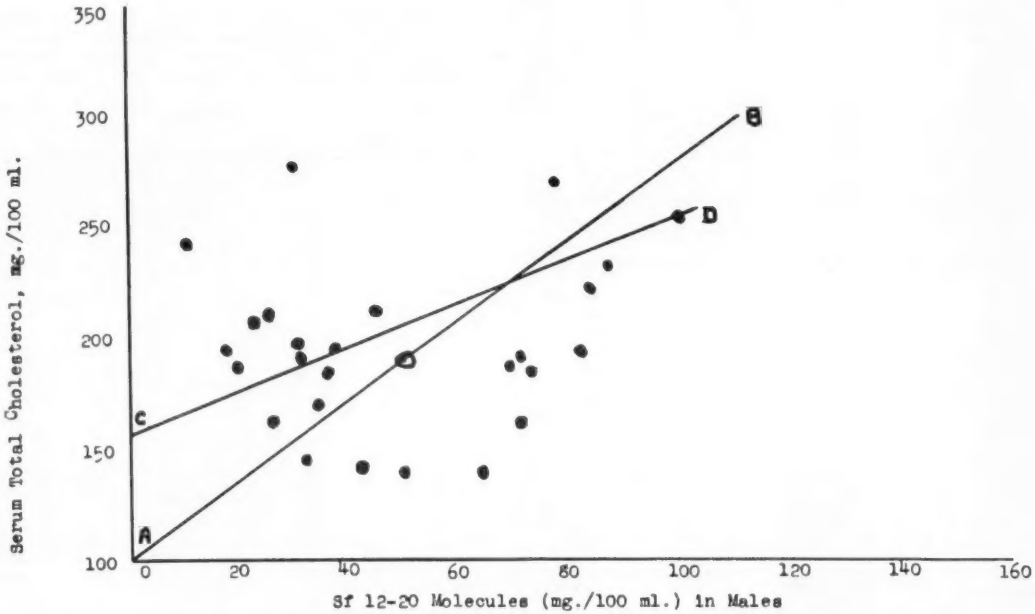

Fig. 4. Scattergram with mean value (A-B) and regression line (C-D) showing a significant positive correlation between the level of serum total cholesterol and Sf 12-20 molecules in "normal" men aged 80-100 years. Regression coefficient (.996). Significant at the 99 per cent level. (p .01).

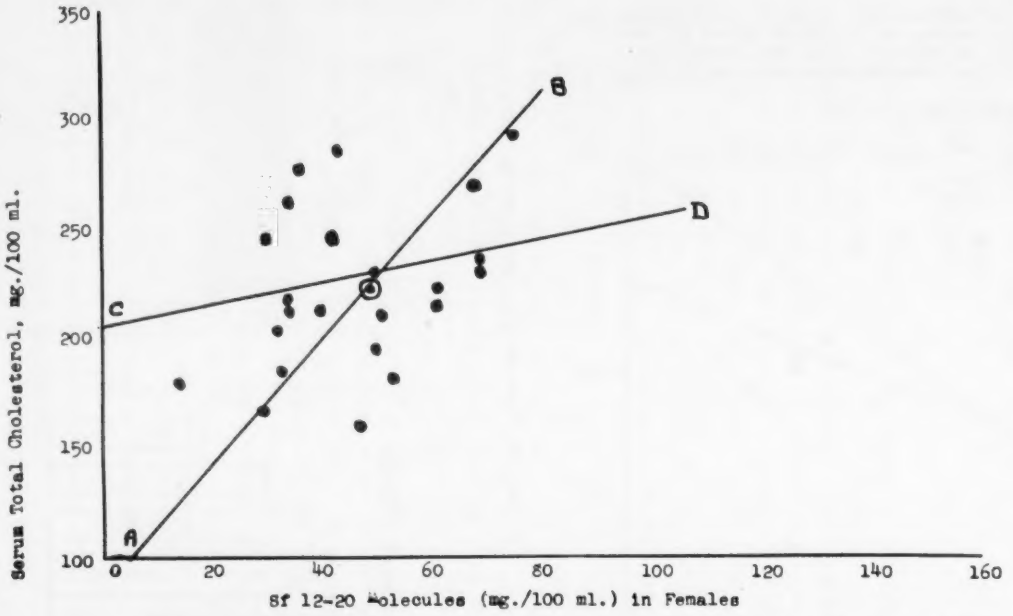

Fig. 5. Scattergram with regression line (C-D) showing a significant positive correlation between the level of serum total cholesterol and Sf 12-20 molecules in "normal" females, aged 80-100 years. Regression coefficient (.52). Significant at the 99 per cent level ($p < .01$). A-B, arithmetic mean values.

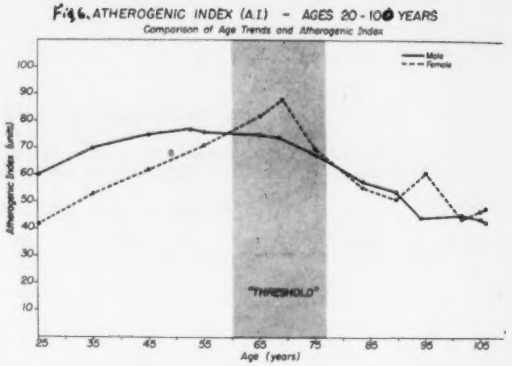

Fig. 6.—The mean value of the atherogenic index is lower in the younger group, with a gradual rise until the "threshold" is attained, followed by a decline until age 100 is reached. The mean atherogenic index value for normal 80- to 100-year-olds, male and female, is 55 units, compared with 70 to 85 units in the middle-age group.

TABLE I. Average Sf 0-12, Sf 12-400 and Atherogenic Index Values Age 20 to 100 Years.

	AGE	Sf 0-12	Sf 12-400	ATHEROGENIC INDEX
MALES	20-29	316	159	59
	30-39	340	201	70
	40-49	361	206	74
	50-59	376	211	75
	60-69	376	196	73
	70-79	362	180	67
	80-85	200	163	58
	86-90	264	157	54
	91-95	230	89	45
	96-100	328	85	48
FEMALES				
	20-29	258	85	46
	30-39	290	121	51
	40-49	324	159	61
	50-59	364	196	71
	60-69	401	260	84
	70-79	374	202	69
	80-85	266	151	56
	86-90	299	128	52
	91-95	329	160	61
	96-100	310	75	44

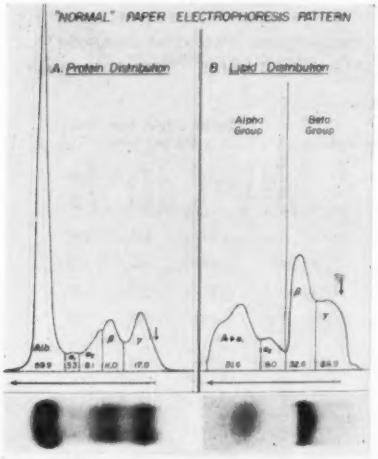

Fig. 7.—Normal pattern: protein distribution: Albumin, 60%; α_1 fraction, 3%; α_2 fraction, 8%; β fraction, 11%; γ fraction, 18%. Lipid distribution: 60% lipids in beta group (corresponds to region of beta and gamma proteins); 40% in the alpha group (corresponds to albumin, α_1 and α_2).

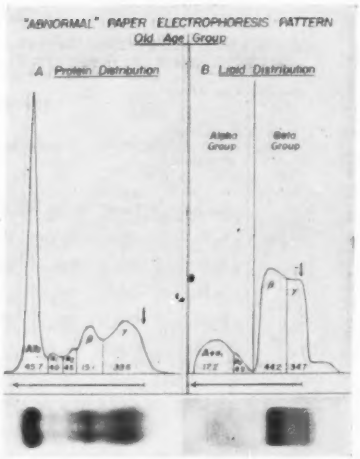

Fig. 8.—Abnormal old age group pattern: protein distribution: γ, high; albumin, low. Albumin, 46%; α_1, 4%; α_2, 4.6%; β, 15.1%; γ, 31%. Lipid distribution: abnormal shift in beta group; 80% lipids in beta group; 20% in alpha group.

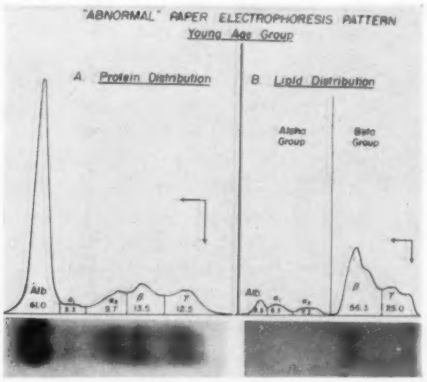

Fig. 9.—Example of an abnormal paper electrophoresis pattern in normal patients, 17 to 46 years of age. *A*, protein distribution, normal. *B*, lipid distribution shows increased beta and decreased alpha group values.

The S_f 0-12 and S_f 12-400 classes of lipoproteins rise from age 25 until the "threshold" is attained, and then there is a reversal of trends. No previous correlated studies in the 80- to 100-year-old group are available for comparisons. Serum lipoprotein determinations of S_f 0-12 and S_f 12-400 class do not demonstrate any correlations with serum cholesterol values (Figs. 1 and 3).

In the male and female patients there is a correlation between total cholesterol and the S_f 12-20 molecules, but not in other fractions. Hypocholesteremia may exist in the same patient with increased standard S_f lipoprotein fractions. (Figs. 4 and 5.)

TABLE II

SERUM LIPID PARTITIONS, Sf LIPOPROTEIN MOLECULES, AND ATHEROGENIC INDEX IN TWO DIFFERENT AGE GROUPS. (MALE AND FEMALE)

A. Old Age Group

			(Increased Values*)							
			Sf Lipoprotein Molecules Mg per cent				Atherogenic Index (Units)	Serum Lipid Partition Mg per cent		
	Female									
No.	Name	Age Years	0-12	12-400	12-20	20-100		Total Lipids	Total Cholesterol	Phospholipids
2	E. V.	80	208	37	15	8	28	487	173	150
3	M. H.	92	335	40	28	6	40	634	266	187
4	A. H.	93	424	213	64	114	80*	575	238	127
5	R. B.	91	431	189	55	102	76*	649	252	152
Mean Average	Female Patients	80-100 Years	305	128	43	46	53.2	645	230	192
	Male									
6	J. L.	90	240	174	39	66	55	521	177	192
7	W. B.	82	284	126	40	28	50	576	198	194
8	M. G.	94	287	150	37	20	55	619	184	201
9	H. C.	94	281	35	28	8	24	596	260	175
10	F. M.	93	444	277	64	73	93*	595	178	190
11	B. M.	89						861	197	218
Mean Average	Male Patients	80-100 Years	293	131	36	43	53	611	203	194

B. Young Age Group

	Male						
12	S. C.	44	366	215	50	132	74
13	J. G.	46	280	97	22	60	45
14	M. M.	33	395	142	46	70	64
Mean Average	———	→	361	206	75	108	74
	Female						
15	I. P.	17	297	90	44	37	45
16	P. R.	25	367	40	31	3	44
17	M. W.	35	473	42	4	33	55
Mean Average	———	→	304	187	53	63	51
For Normal Middle Aged Patients	———	→					861 197 218

The Atherogenic Index: An ideal compendium of the pertinent information on lipoproteins would be a single number descriptive of a person's atherogenic potentialities. This is the atherogenic index, and is derived from the following formula (Fig. 6):

$$\text{Atherogenic Index} = \frac{\text{mg/100 cc. Standard } S_f \text{ 0-12} + 1.75 \times \text{mg/100 cc. Standard } S_f \text{ 12-400}}{10}$$

The average S_f 0-12 and S_f 12-400 lipoprotein molecules and atherogenic index values for ages 20 to 100 are presented in Table I.

Electrophoresis.—One purpose of the investigation was to determine whether the rise in β-globulin in aged patients' sera is related to the increased level of specific macromolecular lipoprotein components. The β-globulin fraction contains an appreciable percentage of serum lipids bound in the form of β-lipoproteins. Some

TABLE [illegible]

PROTEIN AND LIPOPROTEIN DISTRIBUTION IN THE BLOOD SERUM OF HUMAN SUBJECTS BELONGING TO TWO DIFFERENT AGE GROUPS AS DETERMINED BY PAPER ELECTROPHORESIS

A. Old Age Group

No.	Name	Sex	Age Yrs.	Relative Protein Distribution					Ratio	Relative Lipoprotein Distribution		
				Alb.	α_1	α_2	β	γ	A/G	Group α	Group β	Ratio β/α
2.	E. V.	F	80	54.0	4.3	7.88	14.9	19.1	1.17	30.2	70.4	2.3
3.	M. M.	F	92	51.1	4.3	10.0	6.1	28.6	1.05	45.8	50.3	1.1
4.	A. H.	F	93	56.7	4.7	12.7	12.1	13.9	1.31	32.2	67.9	2.1
5.	R. B.	F	91	59.9	3.3	8.1	11.0	17.8	1.49	40.6	59.5	1.4
6.	J. L.	M	90	54.0	6.8	8.0	14.2	17.0	1.17	28.6	71.4	2.5
7.	W. B.	M	82	43.3	4.1	10.9	10.9	30.9*	0.76	40.7	58.8	1.4
8.	M. G.	M	94	52.6	3.9	9.1	12.3	22.3	1.11	34.9	65.6	1.9
9.	H. C.	M	94	43.0	3.8	10.2	11.6	31.4*	0.75	40.1	60.2	1.5
10.	F. M.	M	93	45.7	4.0	4.6	15.1	30.6*	0.84	21.4	78.9*	3.7
11.	B. M.	M	89	42.0	6.9	10.7	18.3*	22.1	0.74	13.6	86.5*	6.3
	Average		90	50.2	4.6	9.2	12.6	23.4	1.04	32.8	66.9	2.4
				B. Younger Age Group								
12.	S. C.	M	44	61.0	3.3	9.7	13.5	12.5	1.56	18.8	81.3*	4.3
13.	J. G.	M	46	a) 54.1	4.8	11.2	13.6	16.3	1.18	33.7	67.3	2.0
				b) 57.8	3.5	6.8	13.3	18.5	1.37	37.1	63.2	1.7
14.	M. M.	M	33	67.8	5.0	6.0	8.5	12.7	2.10	39.8	60.2	1.5
15.	I. P.	F	17	56.1	4.2	6.6	12.2	20.8	1.28	30.1	69.8	2.3
16.	P. R.	F	25	63.9	4.2	5.9	10.5	15.5	1.77	21.1	79.9*	3.7
17.	M. W.	F	35	61.7	3.5	8.5	9.4	16.9	1.61	25.6	75.2	2.9
	Average		33	61.0	4.0	7.6	11.2	15.9	1.59	28.5	71.9	2.7

*Increased Values

correlations between electrophoretic studies and ultracentrifuge results were therefore sought. The extreme simplicity of the apparatus required for the electrophoretic separation of serum proteins and lipid distribution on filter paper makes it possible for such a specialized diagnostic tool to be used more frequently and economically. Three typical studies are illustrated in Figures 7, 8, and 9.

The arithmetic mean values of the serum lipid partitions, S_f lipoprotein molecules, and the atherogenic index in normal patients (young and old) are noted in Table II. This confirms the observations that an increase of the S_f lipoprotein molecules need not be accompanied by an increase in the total cholesterol or lipid partitions, and vice versa (Table II).

The average values by paper electrophoresis for the alpha and beta groups as well as the ratio of the beta to alpha lipoproteins were practically the same in the old age and the younger age groups (Table III).

The increased β-lipoprotein values do not occur in these persons in the old-age group who have increased S_f lipoprotein molecules and increased serum lipid partitions. There is no clear-cut correlation between the chemical serum lipid partitions, S_f lipoprotein molecules by the ultracentrifugal method, and the lipid distribution diagram (lipidogram) by paper electrophoresis.

X-Ray Studies

1. *Thoracic Aorta.*—The roentgenograms of 1000 patients were surveyed for calcification of the thoracic aorta. Posterior-anterior views were studied and meas-

ured. Routine chest films of patients aged 50 to 100 years were charted, and the findings are shown in Figure 10.

It appears that the curves obtained from the serum lipoprotein classes and the atherogenic index do not coincide with the curve of calcification incidence as accurately as they do with the incidence of aortic dilatation. Of the 750 patients aged 50 to 100 years, 50% of the men and 70% of the women showed calcification. In the 80- to 100-year-old group, of 335 patients, 67% of the men and 94% of the women had calcification of the thoracic aorta. Calcification of the thoracic aorta progresses with age in both sexes, starting with a steeply ascending curve which flattens gradually when the higher age groups are reached. This process progresses more rapidly in women than in men. After 60 years the ratio between the calcification in men and women becomes almost 2:3 and remains fairly constant with increasing age, after the "threshold age" (Fig. 10).

Marked differences in width of aortic knob were classified as (1) N, normal width: 3 cm. for women; 3.2 for men; (2) M, moderate widening: 3 to 4.2 cm. for women; 3.2 to 4.5 cm. for men; (3) C, considerable widening: greater than 4.2 cm. for women; 4.5 cm. for men (Figs. 11 and 12).

2. *Abdominal Aorta.*—A survey of 200 patients ranging from 60 to 100 years of age was made. Calcification of the abdominal aorta is slightly less than calcification of the thoracic aorta in comparable groups. Progression and sex differences in calcification of the abdominal aorta follow a pattern similar to that in calcification of the thoracic aorta. There is a greater percentage incidence in the female group (85%) than in the male group (58%) (Fig. 13).

3. *Femoral Arteries.*—Calcification of the femoral arteries is slightly less than that of the aorta. Progression follows a pattern similar to that of the aorta. Progression is more rapid in women (79%) than in men (63%), but sex differences are somewhat less pronounced than in aortic calcifications (Fig. 14).

Comment.—For each age group, the incidence of calcification increases with age, being more advanced in women than in men. The incidence of dilatation of the aorta decreases after age 75, while that of calcification increases. Calcification of the aorta does not coincide with the biochemical findings, whereas dilatation does.

Typical x-ray findings, in patients 80 to 100 years old who demonstrated noticeable declines in the serum lipoprotein classes and blood lipid values, are shown in Figures 15, 16, 17, and 18.

Electrocardiograms

A gradually increasing sclerosis of the coronary vessels occurs as part of the normal aging process. Some changes not acceptable as normal in the young adult may be so considered with advanced age. No hard and fast rule can be laid down as to what may be called normal or abnormal in the aged. There is no characteristic electrocardiographic tracing of old age. Electrocardiograms of 200 patients 80 to 100 years old revealed that 71% of the older group were within normal limits. Almost all showed some degree of left axis deviation. Abnormalities were found in 29%, with right bundle branch block in 11%, conduction disturbances in 7%, old infarctions in 5%, left ventricular strain in 3%, and miscellaneous abnormalities in 3%.

Ballistocardiograms

The ballistocardiograph registers body movements produced by the projection of the instantaneous spatial vector along the head-foot axis and performs according

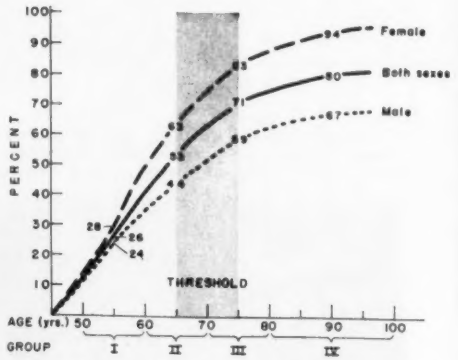

Fig. 10.—Calcification of the thoracic aorta progresses with age more rapidly in females than in males. There is a sharp rise from age 50 until "threshold," then tendency to flattening (750 patients, 50 to 100 years of age).

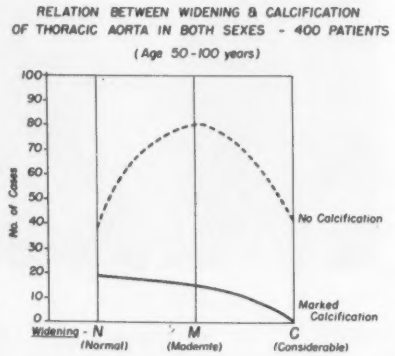
RELATION BETWEEN WIDENING & CALCIFICATION
OF THORACIC AORTA IN BOTH SEXES - 400 PATIENTS
(Age 50-100 years)
No. of Cases
No Calcification
Marked Calcification
Widening - N (Normal) M (Moderate) C (Considerable)

Fig. 11.—Considerable widening of the aortic arch is never associated with marked calcification.

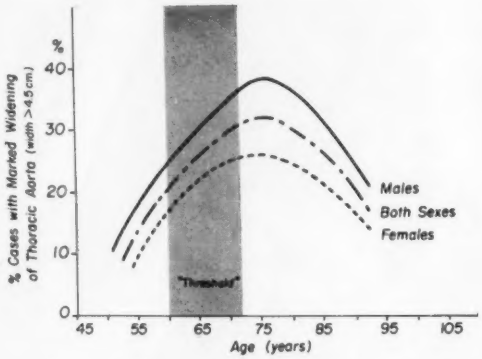

Fig. 12.—Widening of the thoracic aorta progresses with age. The incidence of widening, however, decreases after the "threshold" age is passed. Widening of the thoracic aorta is found more frequently in men than in women, regardless of age.

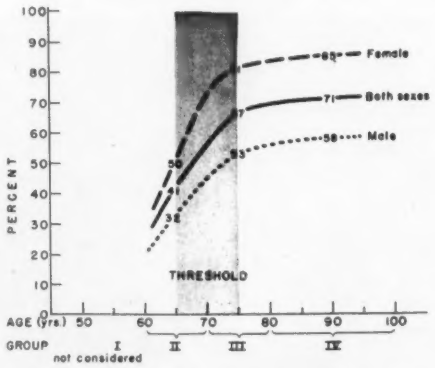

Fig. 13.—Calcification of abdominal aorta in patients 60 to 100 years of age.

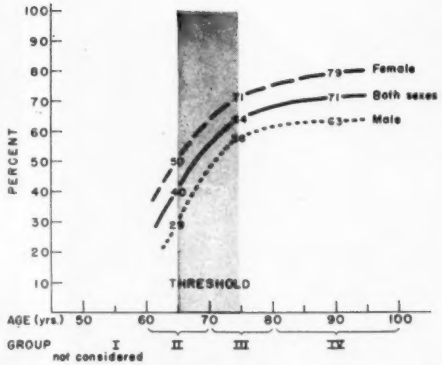

Fig. 14.—Calcification of the femoral arteries in 250 patients 60 to 100 years of age.

Fig. 15.—Marked calcifications in wall of thoracic aorta associated with moderate widening of lumen. There is an increase in size of the left ventricle.

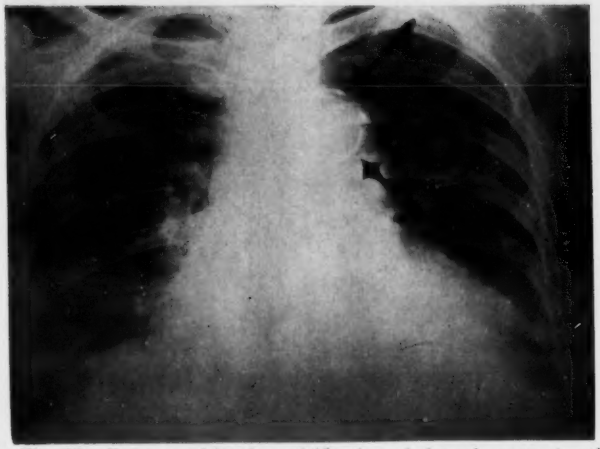

Fig. 16.—Dense semicircular calcification of thoracic aorta (aortic knob). Aorta is moderately widened. Cardiac shadow reveals marked generalized enlargement.

Fig. 18.—Both femoral arteries and branches show marked calcification.

Fig. 17.—Dense calcific plaques in the wall of the abdominal aorta (indicated by upper 2 arrows). There is also calcification of the iliac arteries in front of L4 and L5. The patient is a "normal" atherosclerotic.

to the law of vibration mechanics. Recording techniques, which are still far from perfect, produce curves which are merely the result of the harmonic vibration of the human body, on which are superimposed the motions produced by cardiovascular forces. The techniques, as used in the aged, are greatly open to criticism because of many factors, such as rigidity, fear, inability to relax completely, and bodily distortions so common in the elderly. The distortion of the ballistocardiogram by extracardiac forces—chiefly aortic rigidity—is noticeable in the aged. Fewer than 20% of our records were within normal range.

Eye Studies (Ophthalmoscopy)

Despite normal blood pressure readings, all patients revealed moderate to advanced arteriosclerotic changes of the retinal vessels. These patients may have had some intermittent periods of hypertension, thus having an irreversible change in the retinal vessels similar to that of a hypertensive. Having survived these crises, the patients have been able to carry on with diminishing blood pressure tension values without incurring other retinal pathology.

The tortuosity of the retinal vessels appears first in the periphery. As the degree of arteriosclerosis progresses, tortuosity becomes more evident in the vessels near the optic disk. The degree of arteriosclerotic changes in the retinal vessels may be classified as follows: 1+, tortuosity at the extreme periphery of the vessels; 2+, tortuosity starting two disk diameters from the nerve head, small discrete exudates, and hemorrhage, with some indentation of the crossing vessels; 3+, tortuosity of all the vessels of the retina, with marked indentation where vessels cross, and larger exudates and hemorrhages, extending throughout the retina; 4+, similar to 3+, with closure of several vessels; areas of atrophy, pigmentation, and hemorrhage, and changes in the optic disk, with varying degrees of papilledema.

Pathologic Studies

The changes seen in the aorta and coronary arteries are those which have been characteristically described by many authors as occurring in arteriosclerosis. This term is being used generically, without our entering into the problem of the primacy of intimal or medial lesions, of elastic tissue degeneration, of lipid imbibition, or of ground substance alteration (Figs. 19 and 20).

In the aorta, one finds varying degrees of thickening of the intima by fibrous connective tissue, splitting and hyperplasia of the internal elastic membrane, and "mucoid" degeneration of the intima, most frequently in its deeper layers (Fig. 21). Frequently, comparable changes were present in varying depths of the contiguous media. Also seen was a diminution in metachromatic substance in these areas of the intima and media as well as cholesterol clefts, lipid globules, and calcification. Stippled calcifications were frequently present in the media. In occasional sites, clusters of foam cells were noted in the superficial portions of the intima (Fig. 22). Interestingly enough, they were most prominent in our cases with the lowest atherogenic index.

The coronary artery changes were also qualitatively similar to those seen in the 50- to 80-year-old group, but they were much severer. These changes are similar to those noted in the aorta—the one difference being that the media and internal elastic membrane were frequently bulged and thinned by the underlying arteriosclerotic process rather than being involved by degenerative changes, as in the aorta.

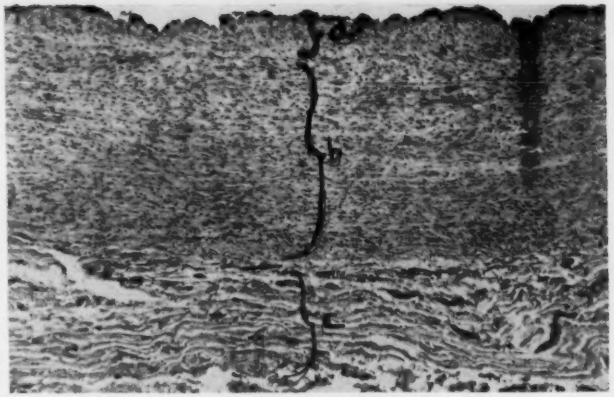

Fig. 19.—Normal section of thoracic aorta in older age group; reduced from mag. × 70. (*a*) Intima; (*b*) media; (*c*) adventitia. This is the usual picture seen in "normal" older persons.

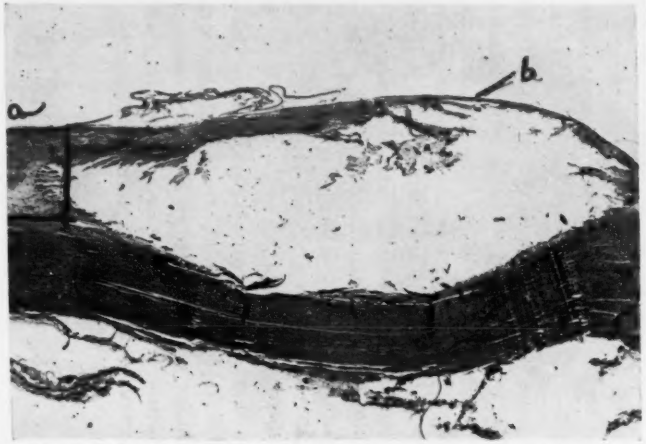

Fig. 22.—Section of calcified atheromatous plaque; reduced from mag. × 18. There is an extremely thin cap of fibrosed intima (*b*). If this cap were torn (premortem or postmortem), an atheromatous ulcer would eventuate.

Fig. 20.—Section of thoracic aorta showing arteriosclerotic changes; reduced from mag. × 70. This Figure is a higher magnification of a part of area (*a*) in Figure 22. (*a*) Lipid-laden macrophages (intima); (*b*) mucoid alterations (media). The elastica is disrupted. There is stippled calcification. (*c*) Adventitia.

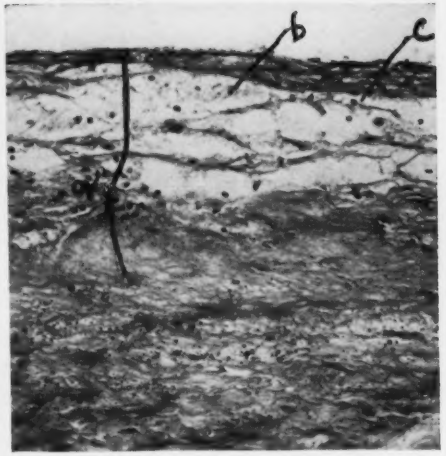

Fig. 21.—(*a*) High-power magnification of a fibrosed intima reduced from mag. × 280. This Figure is a higher magnification of a part of area (*a*) in Figure 20. (*b*) and (*c*) Lipid-laden macrophages. Clear lipid spaces distend cytoplasm of imbibing macrophages. This represents recent lipid imbibition.

Fig. 23.—Aortic arch and thoracic aorta demonstrating severe arteriosclerosis with marked "atheromatous" ulceration. This patient is typical of a large group of 90-year-old persons who had low blood lipids, low serum lipoprotein fractions, and normal ECG tracing and were considered to be "normal atherosclerotics." The x-ray revealed marked calcification, and the aortic arch measured 4.5 cm.

The pathological (autopsy) findings are somewhat equivocal. They show no appreciable correlation with chemical laboratory results but do with x-ray findings. In some of the aortas examined, evidence of lipid imbibition was found in the innermost coats. This is similar to the early changes found in the aortas of rabbits which are fed large amounts of cholesterol, as in the studies of Anitschkow (Fig. 21*b* and *c*).

There was no correlation of the pathologic findings with those of the clinical laboratory. There was good correlation with roentgenogram findings. However, the difference between medial and intimal calcification cannot be differentiated on x-ray examination, as shown in Figures 23, 24, and 25.

CONCLUSIONS AND SUMMARY

This exhibit presents a study of normal persons aged 80 to 100 years, with no previous metabolic, coronary artery, or cardiovascular diseases. Serum lipid partitions, analytical ultracentrifugal lipoprotein fractions, paper electrophoresis (includ-

Fig. 24.—Arch and thoracic aorta, showing severe arteriosclerosis with marked atheromatous intimal changes with ulceration.

ing lipidograms), x-rays, electrocardiograms, ballistocardiograms, and serial pathological findings were correlated and compared with similar studies of younger subjects (25 to 80 years).

A "threshold" occurs in the 60- to 75-year-old group, after which there is a reversal of biochemical and/or physical processes. Correlated x-ray and biochemical data in the presence of microscopic atherosclerosis were found, which are not in agreement with previously accepted criteria (Fig. 26).

Life may be divided into a race of four "hurdles" or groups (Fig 26): (*a*) youth—infectious diseases; (*b*) middle age—coronary and heart diseases; (*c*) late middle age—malignant diseases; "threshold age"—biochemical processes reverse (60 to 75 years); (*d*) old age—frequent accidents.

"Threshold age"—60 to 75 years: Our studies have shown that at the age of 60 to 75 years the trend to increase of total lipids, certain serum lipoproteins, the atherogenic index, and the incidence of aortic dilatation is reversed. These values begin to decline. This is due to some invisible, not clearly understood, barrier.

Fig. 25.—Thoracic and abdominal aorta. Moderate arteriosclerosis with slight atheromatous changes of the thoracic aorta and severe atheromatous changes of the abdominal aorta. Again, as with the preceding changes (Figs. 15, 16, and 17), there were no significant biochemical changes. Moderate x-ray calcification and aortic arch dilatation were found.

Whether it is due to a degenerative process attributable to metabolic and/or enzymatic imbalances can not be answered at present. The values reach the levels found in middle age. These normal aged persons thus acquire their "second youth" again, and this may explain why they attain such an age of 80 to 100 years.

The diagnostic survey and summary of our studies in normal persons aged 80 to 100 years—the methods utilized, the findings obtained, and the clinical values, with new concepts, are shown in Table IV.

New laboratory and technical concepts (Fig. 26): The new laboratory concepts reveal that values of blood lipids, such as total cholesterol and phospholipids, are inconclusive. A ratio of phospholipid to cholesterol (P/C ratio) less than 1.00 does not imply atherosclerosis. The upward trends of values of ultracentrifuge lipoproteins and the atherogenic index become reversed in the "threshold age." Results with electrophoresis (paper method) present no direct correlation with those of the ultracentrifuge methods. There are no typical "electrocardiograms of the aged," since 71% of these persons presented a normal pattern. Ballistocardiograms are unsatisfactory because of technical difficulties caused by rigidity and tremors. Elevated blood pressure readings in the aged usually are not normal.

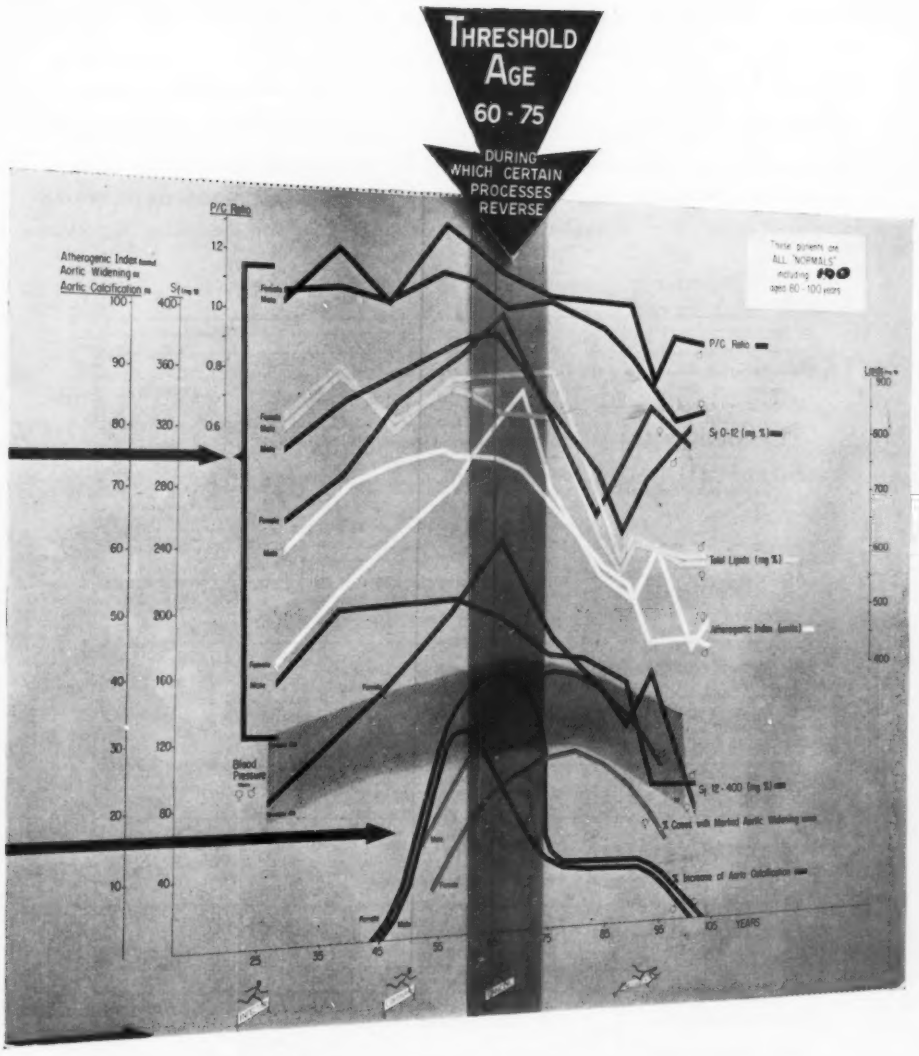

Fig. 26.—Biochemical and roentgenological data in normal persons aged 25 to 100 years. All findings increase until the "threshold age," of 60 to 75, after which there is a decline, or reversal, of trends. The division of life into a race of four "hurdles" or groups is presented.

Ophthalmoscopy (eye ground examination) is a supportive method for diagnosing arteriosclerosis. A classification for the degree of arteriosclerotic changes in the retinal vessels is offered (Table IV).

New roentgenological concepts and interpretations have resulted from this study. Calcification of the aorta progresses more rapidly in women. There is a sharp rise until the "threshold age." Then, there is comparatively a slight increase. Aortic dilatation is more frequent in men. As it reaches the "threshold age," around 70 to

80 years, the incidence decreases with age in both sexes. Marked aortic widening is usually not associated with marked calcification in either sex. Calcification of the aorta does not coincide with the biochemical findngs, while dilatation does.

Pathological (autopsy) findings are somewhat equivocal. They show no appreciable correlation with chemical laboratory findings but do with x-ray findings. In some of the aortas examined, evidence of lipid imbibition was found in the innermost coats. This is similar to the early changes found in the aortas of rabbits

TABLE IV SUMMARY OF RESULTS IN AGE GROUP 80 - 100 YEARS

METHODS	FINDINGS	VALUE
Cholesterol	Slightly elevated in females	?
Cholesterol esters	No significant change	0
Phospholipid	No significant change	0
Total Lipids	Marked decline	?
Creatinine	No significant change	0
Non-protein nitrogen	No significant change	0
Blood count	Slight decrease in RBC and hemoglobin	0
P/C Ratio	Statistically inconclusive	0
Ultracentrifuge	Lipoprotein classes reversed Atherogenic Index reversed	? ?
Electrophoresis	No clear cut correlation with ultracentrifuge methods	?
Chylomicron count	Statistically inconclusive	?
Aortic x-rays	Dilatation of the aorta may be more significant than the presence or amount of calcification	##
Ophthalmoscopy	Possibility of newer classification with relationship of amount of sclerosis to distance from optic disc.	#
Electrocardiogram	71% within normal limits	#
Ballistocardiogram	Technical difficulties still great	?
Pathology	In a state of great flux. Entire status in process of being re-evaluated	?

which are fed large amounts of cholesterol, as in the studies of Anitschkow, and is considered by some to similate "active atherosclerosis."

The Role of the Geriatrician

Our studies have given hope and a nondefeatist attitude in treating geriatric persons. There are many procedures the physician should "do" and "not do" (Table V). Hypertension may be controlled; retinal hemorrhage may be

diminished; tremors and spasticity may be helped. Pain from osteoporosis (thinning of the bones) may be relieved by hormones. Since this is the hurdle (or group) of accidents, these persons must be instructed to minimize accidents. Rehabilitation has become an important aid to comfort these oldsters and alleviate their troubles.

The physician, because of our studies, is warned not to prescribe therapy or perform procedures that may be harmful—not to prescribe low-calorie low-fat

	WHAT THE GERIATRICIAN SHOULD DO	SHOULD NOT DO
DIET	Liberal balanced diet. Correct obesity	Low caloric-low fat diet
LIPOTROPIC AGENTS	Use only if liver is damaged or fatty	Not specific for human atherosclerosis
HYPERTENSION	Control by anti-hypertensive agents	Should not be disregarded. Elevated blood pressure in aged abnormal.
PERIPHERAL VASCULAR CONDITIONS	Deliberate examination. Vasodilators-proper hygiene and physical measures. Feet lowered; skin soft; shoes wide.	Extremes of temperature locally. No tight or elastic bandages.
OPTHALMOLOGY	Examination for cataracts, glaucoma, vitreous opacities and retinal changes	Atropine for dilatation and examination of eyes.
RETINAL HEMORRHAGE	Water soluble bio-flavinoid compounds	Local eye applications of extreme heat and cold. Promiscuous use of antibiotics locally.
AGITATION	Chlorpromazine and chloral usually safe and effective.	Barbiturates in aged may cause further excitation and other harmful effects
TREMOR-SPASTICITY	Proper selection and combination of drugs for Akinesia, rigidity and tremor.	Immobilization; splinting; allow distorted body posture.
HORMONES	Androgens and estrogens (simultaneously) often relieve pain from osteoporosis	Analgesics alone merely mask osseous pain and of no direct value.
ANTICOAGULANTS	Heparin safer than oral anticoagulants	Oral anticoagulants dangerous in liver, renal, and ulcerating pathology.
ACCIDENTS	Instructions - to minimize accidents such as hip fractures - common type in the aged.	Allow aged to vegetate.
REHABILITATION	Graded physical exercise and mental occupation. Well planned environment.	Adapt a defeatist attitude and "do nothing".

diets; not to give lipotropic agents, except if the liver is damaged or fatty; not to ignore elevated blood pressure; not to use atropine or local antibiotic preparations promiscuously for eye conditions; not to give excessive barbiturate preparations. Do not immobilize nor splint, nor permit these patients to assume a distorted body posture. Oral anticoagulants are dangerous in liver, renal, and ulcerating (ulcer) pathology. Do not allow the aged to vegetate, and do not assume a "do nothing" attitude.

REFERENCES

1. Goldbloom, A. A.: Clinical Studies of Blood Lipid Metabolism: I. Normal Blood Lipid Variations of Phospholipids, Neutral Fats, Total Lipids, and Lipid Fraction Percentages, Am. J. Digest. Dis. **19**:9, 1952.

2. Pomeranze, J.; Boyd, L. J., and Goldbloom, A. A.: Newer Clinical and Laboratory Studies in the Aged: I. Serum Lipid Partitions, A. M. A. Arch. Int. Med. **91**:740, 1953.

3. Eiber, H. B.; Goldbloom, A. A.; Boyd, L. J.; Chapman, I., and Deutschberger, O.: Newer Clinical and Laboratory Studies in the Aged: II. Correlated Serum Lipid Partitions and Lipoprotein Molecules (S_f 0-400) in Patients 80-100 Years of Age; Preliminary Report, Bull. New York Acad. Med. **30**:719, 1954.

4. Goldbloom, A. A.; Eiber, H. B.; Chapman, I.; Deutschberger, O., and Loewe, W. R.: Newer Clinical and Laboratory Studies in the Aged: IV. Atherosclerosis in Normal Patients 80-100 Years of Age, Circulation **10**:605, 1954.

5. Goldbloom, A. A., and Pomeranze, J.: Clinical Studies in Blood Lipid Metabolism: IV. Abnormal Lipid Metabolism and Atherosclerosis; Preliminary Report, Am. J. Digest. Dis. **19**:281, 1952.

6. Goldbloom, A. A.: Clinical Studies in Blood Lipid Metabolism: VI. Serial Serum Lipid Partitions in Patients with Chronic Coronary Artery Disease, Am Pract. & Digest Treat. **3**:799, 1952.

7. Goldbloom, A. A., and Eiber, H. B.: Clinical Studies in Blood Lipid Metabolism: XI. Clinical Significance of the Ratio of Phospholipid to Total Cholesterol (P/C Ratio), Bull. New York M. Coll. **16**:32, 1953.

8. Gofman, J. W.; Strisower, B.; De Lalla, O.; Tamplin, A.; Jones, H. B., and Lindgren, F.: Index of Coronary Artery Atherogenesis, Mod. Med. **21**:119; 138, 1953.

9. Ackerman, R. F.; Dry, T. J., and Edwards, J. E.: Relationship of Various Factors to Degree of Coronary Atherosclerosis in Women, Circulation **1**:1345, 1950.

10. Eiber, H. B.; Goldbloom, A. A.; Boyd, L. J., and Deutschberger, O.: New Biochemical and Physical Aspects of the 80 to 106 Year Old Patients, shown as a Scientific Exhibit, at the Annual Convention of the Medical Society of the State of New York, New York, May 10-14, 1954.

11. Goldbloom, A. A., and Eiber, H. B.: Newer Clinical and Laboratory Studies in the Aged: VI. Serum Lipid Partitions, Lipoproteins and Atherogenic Index, in "Normal" Subjects, 80-100 Years of Age, J. Am. Geriatrics Soc. **3**:367, 1955.

12. Eiber, H. B.; Goldbloom, A. A.; Chapman, I.; Deutschberger, O., and Loewe, W. R.: Newer Clinical and Laboratory Studies in the Aged: VIII. An Outline of the Newer Methods of Study of Atherosclerosis with Emphasis on 80-100 Year Age Group, Geriatrics **10**:213, 1955.

13. Goldbloom, A. A.: Newer Clinical and Laboratory Studies in the Aged: V. Lipidogram by Paper Electrophoresis in "Normal Patients" 80-100 Years of Age, Am. J. Digest. Dis. **22**:51, 1955.

14. Goldbloom, A. A.; Boyd, L. J., and Stern, K. G.: Newer Clinical and Laboratory Studies in the Aged: XV. Studies on the Lipoprotein Distribution in Normal Subjects as a Function of Age and Sex as Determined by Paper Electrophoresis, to be published.

15. Deutschberger, O.; Goldbloom, A. A., and Eiber, H. B.: Newer Clinical and Laboratory Studies in the Aged: X. Roentgenological Changes of the Aorta and Its Branches in Correlation with the Newer Biochemical Methods, Circulation **12**:495, 1955.

16. Dock, W.: Value of Lateral Ballistocardiograms in Differentiating Aortic Tortuosity, Am. J. M. Sc. **228**:125, 1954.

17. Loewe, W. R.; Goldbloom, A. A., and Eiber, H. B.: Newer Clinical and Laboratory Studies in the Aged: XVII. Funduscopic Changes in Patients 80-100 Years of Age, to be published.

18. Chapman, I.; Goldman, A. A.; Mirrer, G., and Eiber, H. B.: Newer Clinical and Laboratory Studies in the Aged: XIV. Gross and Histological Autopsy Findings Correlated with Lipoproteins, in Normal Subjects, Aged 80-100 Years, to be published.

19. Goldbloom, A. A.; Eiber, H. B., and Boyd, L. J.: Clinical Studies in Blood Lipid Metabolism: XI. Effect of Lipotropic Agents on Serum Lipid Partitions in 50 Patients with Generalized Atherosclerosis; A 3-Year Study, Am. J. Digest. Dis. **21**:152, 1954.

20. Loewe, L., and Eiber, H. B.: Anticoagulation Therapy with Heparin in the Management of Coronary Artery Thrombosis and Its Complications, Am. Heart J. **37**:701, 1949.

21. Eiber, H. B.: Combined Chlorpromazine-Rauwolfia Serpentina Therapy in Essential Hypertension, J. A. M. A. **158**:730, 1955.

22. Eiber, H. B.; Goldbloom, A. A.; Liberti, D. H., and Garip, F.: Hypertension in the Aged, shown as a Scientific Exhibit, at the Twenty-Eighth Annual Graduate Fortnight, New York Academy of Medicine, New York, Oct. 10-21, 1955.

23. Goldbloom, A. A.: Newer Clinical and Laboratory Studies in the Aged: IX. Treating Geriatric Patients, Postgrad. Med. **18**:facing p. A-33, 1955.

24. Goldbloom, A. A.; Eiber, H. B., and Danishefsky, I.: Newer Clinical and Laboratory Studies in the Aged: XI. Chemical Studies of the 80-100 Year Old Group, J. Gerontol. **10**:467, 1955.

25. Goldbloom, A. A.; Eiber, H. B., and Boyd, L. J.: Newer Clinical and Laboratory Studies in the Aged: XII. General Management of Normal Individuals After the Age of 80, J. Am. Geriatrics Soc., to be published.

26. Goldbloom, A. A.; Eiber, H. B., and Danishefsky, I.: Newer Clinical and Laboratory Studies in the Aged: XIII. Chemical Studies of the 80-100 Year Old Normal Group, J. Gerontol., to be published.

MÖNCKEBERG'S ARTERIOSCLEROSIS

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MÖNCKEBERG'S arteriosclerosis is a clinically benign form of calcification of the blood vessels. Needless anxiety results from failure to differentiate this condition from intimal arteriosclerosis. Intimal arteriosclerosis often goes on to progressive occlusion of the blood vessels and carries an unfavorable prognosis. In Mönckeberg's arteriosclerosis, thrombosis of the blood vessels in the extremities does not occur, and in patients who have been observed for many years there has been no tendency to develop impaired circulation.

The clinical characteristics that distinguish Mönckeberg's arteriosclerosis from other forms are extreme calcification of the arteries of the lower extremities in young and middle-aged persons who have no symptoms or signs of impaired circulation. Calcification of the blood vessels is usually discovered by accident when a roentgenogram is made for arthritis, fracture, or some other bone or joint condition. There are no complaints of coldness or pain in the legs or difficulty in walking. All pulsations are easily felt in both feet and are normal in size. Oscillometric and temperature studies indicate a normal blood flow.

The prognosis in Mönckeberg's arteriosclerosis is good. There is no tendency to develop intermittent claudication, ulceration, or gangrene. No treatment of any kind is necessary. Nocturnal leg cramps occur in one-third of the cases and can be promptly relieved by calcium lactate given orally.

Pathologically, Mönckeberg's arteriosclerosis is characterized by a deposit of calcium in the media of the arteries, believed to be due to calcific dystrophy of the media ground substance. There is no thickening of the intimal layer, which is the most striking feature of intimal arteriosclerosis, and the blood vessel lumen is therefore not narrowed. The surface of the intima remains uninjured, and thrombosis does not occur.

Roentgenologically, typical cases show dense uniform calcification, which outlines the major arteries and their branches. The calcium appears to be deposited in transverse lines, giving the appearance of a chain of rings similar to a goose neck. In contrast, calcification in intimal arteriosclerosis is patchy, dispersed, and tends to be deposited in the long axis of the blood vessels.

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MÖNCKEBERG'S ARTERIOSCLEROSIS
A NON-OCCLUSIVE ARTERIAL DISEASE

Mönckeberg's Arteriosclerosis is a clinically benign form of calcification of the blood vessels which occurs in young or middle-aged people and is clearly different from intimal arteriosclerosis.

It is usually discovered by accident when an X-ray is made for some other condition. Patients with Mönckeberg's Sclerosis have no symptoms or signs of impaired circulation and when observed for many years do not show occlusion of peripheral arteries.

The X-ray appearance is distinctive. Mönckeberg's Sclerosis is benign and requires no treatment.

MALE, AGE 47

No intermittent claudication. All pulses normal in both feet. Oscillometric reading: 6 at both ankles.

MALE, AGE 58

Intermittent claudication in both legs for two years, after walking three blocks. Both femoral pulses present. Both popliteal pulses absent. Oscillometric reading: left calf 1, left ankle ¼, right calf 1½, right ankle ½.

MALE, AGE 44

No intermittent claudication. All foot pulses present. Oscillometric reading: 5.5 at both ankles.

MALE, AGE 55

Intermittent claudication in the left leg for one year after walking three blocks. The left femoral pulse is present; the left popliteal and all foot pulses are absent. Oscillometric reading: left calf ¾, left ankle ¼, right calf 2½, right ankle 1½.

COMPARATIVE PATHOLOGY and ETIOLOGY

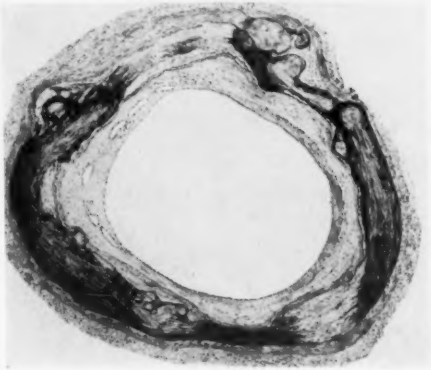
	MÖNCKEBERG'S SCLEROSIS	ARTERIOSCLEROSIS OBLITERANS
SITE	Chiefly in lower extremities.	Chiefly in coronary, cerebral, renal arteries and in aorta.
LOCALIZATION	Media of artery.	Intima and media of artery.
CHARACTERISTICS	Primary deposition of calcium granules diffusely in media ground substance; secondary atrophy of media muscle fibers; occasional thinning of intima.	Hyaline and lipid degeneration with thickening of intima, splitting of internal elastic membrane; secondary calcification in areas of fatty degeneration or necrosis, in intima and media.
THROMBOSIS	Not seen.	Frequent complications
ETIOLOGY	Disturbance of calcium metabolism ?	Disturbance of lipid metabolism ? Arterial stress ? (In cases of hypertension)

COMPARATIVE CLINICAL CHARACTERISTICS

	MÖNCKEBERG'S SCLEROSIS	ARTERIOSCLEROSIS OBLITERANS
INCIDENCE	Infrequent. (About 1% of all peripheral arterial disease cases).	Frequent. (About 90% of all peripheral arterial disease cases.
AGE OF ONSET	Young or middle aged.	Middle aged or old.
SEX	Male to female — 60:1.	Male to female — 6:1
SYMPTOMS	No intermittent claudication, but night cramps occur frequently.	Intermittent claudication and other symptoms of impaired circulation
PHYSICAL FINDINGS	All pulses present and normal in size. Oscillometer readings normal.	Pulses diminished or absent. Oscillometer readings reduced.
CIRCULATION	Blood flow normal at rest. Vascular reserve normal	Blood flow normal or reduced at rest. Vascular reserve reduced.
BLOOD PRESSURE	Normal.	Frequently elevated.
X-RAYS	Extensive, diffuse calcification in transverse bands.	Irregular, patchy calcification in longitudinal axis.
ARTERIOGRAPHY	Normal or increased lumen, intima smooth.	Narrowed, irregular or occluded lumen.
COURSE	Benign and non-occlusive.	Often unfavorable with progressive occlusion.

With advancing age, intimal sclerosis may develop in patients with Mönckeberg's Sclerosis, giving combined pictures. To obtain a clear concept of uncomplicated Mönckeberg's Sclerosis, the disease should be studied in young people.

COMPARATIVE PATHOLOGY

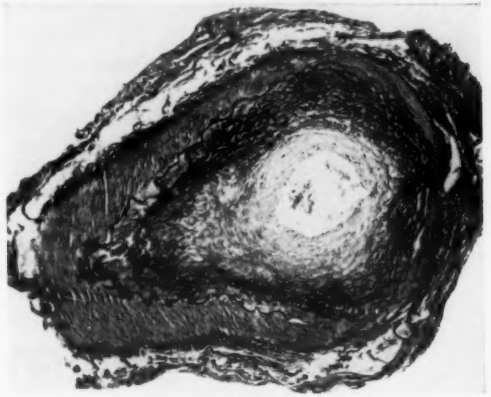


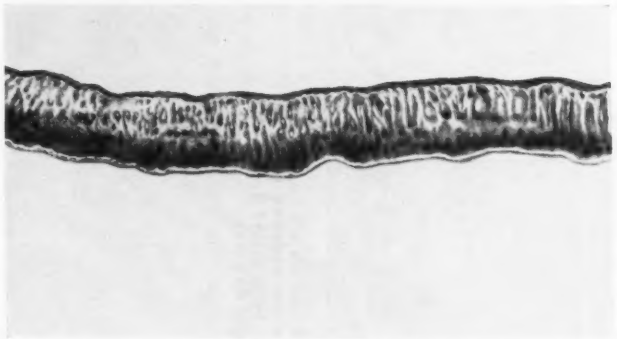
MÖNCKEBERG'S SCLEROSIS

Section of femoral artery. Note intima of normal thickness and smooth, preserved internal elastic membrane, calcification of media, and absence of inflammatory reaction.

ARTERIOSCLEROSIS OBLITERANS

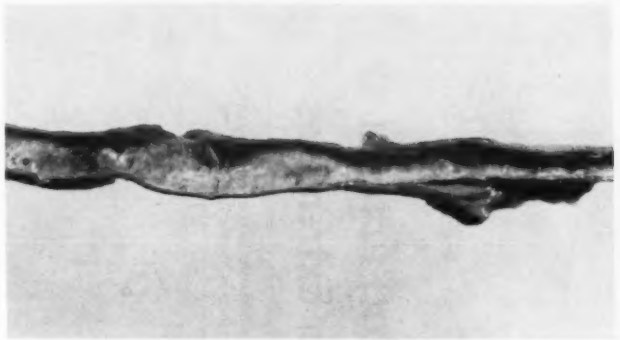
Section of renal artery. Note thickening of intima with narrowing of artery lumen, splitting up and segmentation of internal elastic membrane, and thickening of media.





MÖNCKEBERG'S SCLEROSIS

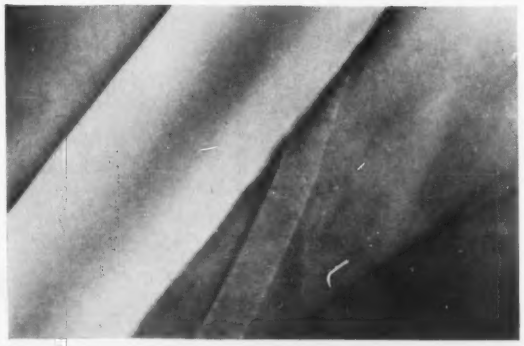
Femoral artery, opened. Note smooth intima with normal artery lumen and horizontal bands of media calcification (goose gullet).



ARTERIOSCLEROSIS OBLITERANS

Femoral artery, opened. Note normal portion at left as compared with diseased portion at right. Thickening of intima with narrowing of artery lumen, deposits of cholesterol and hyaline material into the intima and ulceration, and calcification of the media in longitudinal axis of blood vessel.

X-RAY APPEARANCE



MÖNCKEBERG'S SCLEROSIS

X-ray of femoral artery.

Note fine diffuse calcification in horizontal bands (goose gullet).

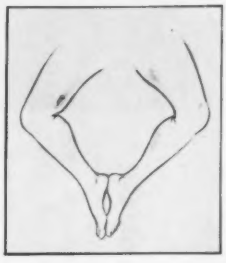
ARTERIOSCLEROSIS OBLITERANS

X-ray of femoral artery.

Note patchy dense calcification in longitudinal axis of vessel.

Positions for Visualizing Arterial Calcifications in the Lower Extremities

To show calcifications in the arteries in front of and behind the ankles.



Patient sits on table, heels and toes together, knees as far apart as possible.

To show calcifications in arteries in the region of the interosseous membranes.

Patient lies prone. The foot is turned in about 45 degrees. If patient is able to turn both feet in so that they make an "X" and are not too far apart, both legs may be taken on a single film. If not, two separate exposures must be made, one of each leg turned in, so the foot is about 45 degrees from horizontal.

To show calcifications in the femoral and popliteal areas.

Patient lies on left side with the thighs medial surface up and knee moderately bent. The extremity not being X-rayed is moved aside, so as to be out of the picture.

To show calcifications in the femoral and popliteal areas.

Patient lies on right side with the thighs medial surface up and knee moderately bent. The extremity not being X-rayed is moved aside, so as to be out of the picture.

UNCOMPLICATED MÖNCKEBERG'S SCLEROSIS

STATISTICAL DATA

TOTAL NUMBER OF CASES		57
SEX:	Male	56
	Female	1
AGE WHEN FIRST DIAGNOSED		27 to 69
ASSOCIATED CONDITIONS:		
	Osteo-arthritis of spine	6
	Renal calculi	2
	Diabetes mellitus	2
	Submandibular calculi	1
	Paget's Disease	1
	Acromegaly	1
	Gout	1
FOLLOW-UP AVERAGE	(from 1 to 18 years)	6½ years

PROGNOSIS and TREATMENT

Thrombosis of peripheral arteries has not been noted in any of our cases

Gangrene has never developed.

No case ever required amputation.

No treatment is necessary.

Nocturnal leg cramps occur in one-third of cases and can be promptly relieved by calcium lactate given orally.

News and Comment

ANNOUNCEMENTS

Survey of Internal Medicine.—A thirteen-part seminar consisting of a survey of the field of internal medicine by means of lectures and case demonstrations in the various medical specialties is being offered from April 9 through June 1 by the Post-Graduate Medical School, a unit of the New York University-Bellevue Medical Center. The seminar may be taken in a whole by physicians wishing to prepare for Board examinations or in part by those who desire a review of particular subjects.

The seminar is given under the direction of Prof. Charles F. Wilkinson Jr. The class is limited to twenty. Tuition for the entire course is $250.00.

The individual sections of the course are as follows: Arthritis and Allied Rheumatic Disorders, Allergy, Cardiology, Clinical Hematology, Clinical Electrocardiography, Normal and Pathological Physiology: Functional and Chemical Aspects, Problems in Diagnosis, Acute and Chronic Diseases of the Chest, Endocrinology, Diseases of the Liver and Biliary Tract, Gastroenterology, Nephritis and Hypertension, and Peripheral Vascular Disease.

Further information and applications may be obtained from the Dean, Post-Graduate Medical School, 550 First Ave., New York 3.

Eleventh Annual Schering Award Competition.—The Schering Award has begun its eleventh annual program for medical students in the United States and Canada.

Students are invited to participate by selecting one of three suggested subjects and submitting papers to the Schering Award Committee, Bloomfield, N. J. Both a $500 first prize and a $250 second prize are offered for each of the three subjects. Decisions are made by a group of judges who are authorities in their respective fields. In addition, every participant in the contest receives a professionally useful gift.

The three subjects for 1956, announced by C. J. Szmal, M.D., chairman of the Schering Award Committee, are the following:

1. The Clinical Use of Adrenocortical Steroids in Collagen Diseases
2. Metabolic Aspects of the Aging Process
3. New Applications of Antihistamines in Medicine and Surgery

Literature and entry forms are being distributed in the medical schools. Students who are interested in participating, either individually or in teams, should submit their entry forms before July 1, 1956, and manuscripts must be postmarked not later than Sept. 30, 1956.

Research in Allergy and Infectious Diseases.—An expanded program of research in allergy and infectious diseases has been announced by Dr. Leonard A. Scheele, Surgeon General of the Public Health Service, U. S. Department of Health, Education, and Welfare.

This program will be administered by the National Microbiological Institute, which is being redesignated as the National Institute of Allergy and Infectious Diseases, Dr. Scheele said. The Institute will also support long-term basic studies in these fields through grants to research scientists in the Nation's universities and medical schools. An increase of $3,200,000 will be sought for this program for fiscal year 1957.

"The renaming of the Institute," the Surgeon General said, "reflects the importance of the new research program on allergies and the close relationship of such research with the study of infectious diseases. Investigations of allergy are closely allied to the science of immunology, which is also fundamental to investigation of the infectious and parasitic diseases."

A separate national advisory council on allergy and infectious diseases is being established to make recommendations to the Surgeon General regarding the new grant and training activities. Heretofore, the National Advisory Health Council has advised the Surgeon General on grants for infectious disease research as well as grants for research in other medical and public health fields which are not covered by a specific Institute.

International Society of Hematology, Sixth Congress.—The time and location of the Congress will be different from the original announcement. The date has been moved forward one week, to Aug. 26-Sept. 1, inclusive. The convention site has been shifted to the Hotel Somerset, Boston.

The officers of the Congress are as follows: Dr. William Dameshek, President; Dr. James L. Tullis, Vice-President and Treasurer; Dr. William C. Moloney, Secretary; Dr. A. Richardson Jones, Assistant Secretary; Dr. Frank Gardner, Assistant Treasurer.

The Sixth Congress of the International Transfusion Society, under the Presidency of Dr. I. S. Ravdin, will be held on Sept. 3-5, inclusive, also at the Hotel Somerset. Combined sessions of the two Congresses are tentatively scheduled for Saturday, Sept. 1, and Monday, Sept. 3. This will permit integration of the immunohematology part of both programs in joint sessions.

The official Travel Agency for the Congress is the World Travel Plan Corp., affiliate of the Hotel Plan of Switzerland. Arrangements for travel may be made directly with World Travel Plan Corp., 125 E. 50th St., New York 22.

Among the speakers who so far have accepted assignments are the following: Leukemia: Joseph H. Burchenal, New York; Giovanni Di Guglielmo, Rome; Alexander Haddow, London; Antoine Lacassagne, Paris; R. Latarjet, France; Samuel Martin, Durham, N. C.; Michael B. Shimkin, Bethesda, Md.; William N. Valentine, Los Angeles. Nucleonics: W. M. Court Brown, London; B. Chr. Christensen, Copenhagen; Clement Finch, Seattle; Leonard Hamilton, New York; W. V. Mayneord, London; Edward H. Reinhard, St. Louis; Joseph F. Ross, Los Angeles; Louis Wasserman, New York. Hemorrhagic Disorders: Tage Astrup, Copenhagen; Kenneth M. Brinkhous, Chapel Hill, N. C.; Erwin Deutsch, Vienna; F. Koller, Zurich; Oscar D. Ratnoff, Cleveland; Walter H. Seegers, Detroit. Anemia: Sheila Callender, Oxford; William B. Castle, Boston; J. B. Marshall Chalmers, Birmingham, England; Sir Stanley Davidson, Edinburgh; Conrad Gasser, Zurich; R. H. Girdwood, Edinburgh; Ludwik Heilmeyer, Freiburg, i. Br.; Hermann Lehmann, London; Carl V. Moore, St. Louis; James Neel, Ann Arbor, Mich.; Wolf W. Zuelzer, Detroit. Immunohematology: J. F. Ackroyd, London; Jean Bernard, Paris; William C. Boyd, Boston; Jean Dausset, Paris; Sabine Filitti-Wurmser, Paris; F. L. J. Jordan, Utrecht; P. Mieschler, Basel; Sven Moeschlin, Solothurn, Switzerland.

Three simultaneous multiple sessions and panel (group) discussions will be held each afternoon (except Wednesday). Ten-minute papers will be followed by discussion. Those desiring to submit papers will please send abstracts (up to 300 words) by March 1, 1956.

Topics in Clinical Medicine.—The Department of Medicine of The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine is offering "Topics in Clinical Medicine," a six-day postgraduate course for physicians primarily interested in internal medicine, May 7 to 12, 1956. The course is under the direction of Dr. A. M. Harvey, professor and head of the department of medicine, and all formal sessions will be held in Hurd Memorial Hall, at the Hospital.

The discussions will deal with recent and significant advances in areas of general clinical interest, and all presentations will be related to the diagnosis and management of patients. Where possible, discussions will be illustrated by clinical demonstrations. The mornings will be generally given over to consideration of specific disease problems, and the afternoons, to symposia and panel discussions devoted to the broad fields of hematology, cardiovascular-renal abnormalities, disorders of connective tissue, infectious disease, and endocrine and metabolic disturbances. Several points of view will be represented on each panel, with adequate time reserved for questions and general discussion.

A clinical pathological conference will be held during the course of the week, preceded by a discussion of "The Approach to Differential Diagnosis." The course will be brought to a conclusion at Medical Grand Rounds, at which interesting cases selected from the wards will be presented.

Registration for the course will be limited to 150 physicians. Registration blanks and further information may be obtained by writing to Dr. Philip A. Tumulty, Department of Medicine, The Johns Hopkins Hospital, Baltimore 5.

Regional Meeting of the American College of Gastroenterology.—A regional meeting of the Southern Region of the American College of Gastroenterology will be held in New Orleans, on Sunday, April 8, 1956. The Scientific Sessions will be held in the auditorium of the Louisiana State University School of Medicine, commencing at 2:00 p. m.

Members of the medical profession are cordially invited to attend. A copy of the program may be obtained from the Secretary, American College of Gastroenterology, 33 West 60th St., New York 23.

The Third National Cancer Conference.—The American Cancer Society and the National Cancer Institute of the Public Health Service, Department of Health, Education, and Welfare, will jointly sponsor the Third National Cancer Conference, in Detroit, June 4, 5, and 6. More than a thousand research scientists and clinicians, including many from foreign countries, are expected to attend.

The opening session of the conference, in the Sheraton-Cadillac Hotel, will feature addresses by Dr. John R. Heller, Director of the National Cancer Institute, and Dr. Charles S. Cameron, Medical and Scientific Director of the American Cancer Society. Morning and afternoon sessions of the three-day meeting will begin with a general session, at which a subject of broad interest will be presented by an outstanding speaker. The general sessions will then break into various symposia to discuss cancer of different body sites, such as lung, gastrointestinal tract, and breast.

Copies of the conference program and advance registration cards may be obtained from the National Cancer Conferences Coordinator, American Cancer Society, 521 West 57th St., New York 19. All physicians are invited to attend.

PERSONAL

Dr. Samuel Preston Martin.—Dr. Samuel Preston Martin will arrive from Durham, N. C., April 1 to begin his duties as new head of the department of medicine in the College of Medicine at the University of Florida. He also will be coordinator of the J. Hillis Miller Health Center Study, which is supported by the Commonwealth Fund of New York.

Until his appointment at the University, by President J. Wayne Reitz, Dr. Martin was associate professor of medicine and assistant professor of bacteriology at Duke University School of Medicine in Durham, where he was a Markle Scholar from 1950 to 1955.

Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOKS RECEIVED

Cybernetics: Circular Causal and Feedback Mechanisms in Biological and Social Systems; Transactions of the Tenth Conference, April 22, 23, and 24, 1953. Edited by Heinz Von Foerster; Assistant Editors, Margaret Mead and Hans Lukas Teuber. Price, $2.75. Pp. 100, with one illustration and one photograph. Josiah Macy, Jr. Foundation Publications, 16 West 46th St., New York 36, 1955.

Congenital Heart Disease: Report of the Fourteenth M & R Pediatric Research Conference at Los Angeles, Nov. 17-19, 1954. Edited by F. W. Heggeness, Ph.D., M.D. Pp. 118, with 28 illustrations and 10 tables. M & R Laboratories, Columbus 16, Ohio, 1955.

The Role of Algae and Plankton in Medicine. By Morton Schwimmer, M.D., and David Schwimmer, M.D., F.A.C.P. Price, $3.75. Pp. 85. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

The Complete Medical Guide. By Benjamin F. Miller, M.D. Price, $4.95. Pp. 914, with over 150 illustrations. Simon & Schuster, 630 Fifth Ave., New York 20, 1956.

Atlas und kurzgefasstes Lehrbuch der Phonokardiographie und verwandter Untersuchungsmethoden. By Priv.-Doz. Dr. Med. K. Holldack and Dr. Med. D. Wolf. Price, $11.80. Pp. 171, with 179 illustrations. Georg Thieme, Herdweg 63, (14a) Stuttgart, Germany, 1956.

Differentialdiagnose innerer Krankheiten. By Dr. Robert Hegglin. Price, $16.65. Pp. 678, with 372 illustrations. Georg Thieme, Herdweg 63, (14a) Stuttgart, Germany, 1956.

Lehrbuch der Verdauungskrankheiten. By Prof. Dr. Med. Norbert Henning. Price, $18.35. Pp. 562, with 335 illustrations. Georg Thieme, Herdweg 63, (14a) Stuttgart, Germany, 1956.

Vascular Surgery in World War II. Edited by Daniel C. Elkin, M.D., and Michael E. DeBakey, M.D. Price, $4.25. Pp. 465, with 56 illustrations and 51 tables. Medical Department, United States Army, Washington 25, D. C., 1955.

Cancer of the Lung. By Milton B. Rosenblatt, M.D., and James R. Lisa, M.D., and others. Price, $15.00. Pp. 330, freely illustrated. Oxford University Press, 114 Fifth Ave., New York 11, 1956.

The Diabetic's Cookbook. By Clarice B. Strachan. Price, $6.50. Pp. 304. The Medical Arts Publishing Foundation, Houston, Texas, 1956. Distributed by University of Texas Press, Austin 12, Texas.

A. M. A. Scientific Exhibits 1955. Sponsored by Council on Scientific Assembly, A. M. A. Price, $20.00. Pp. 784, profusely illustrated. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

Personal Health Measures and Immunization, Vol. III. Edited by Col. John Boyd Coates, Jr. (MC), and Ebbe Curtis Hoff, Ph.D., M.D. Price, $3.25. Pp. 394, with 6 illustrations, 29 tables, and 5 charts. Medical Department, United States Army, Washington 25, D. C., 1955.

Manuale di fisiopatologia. By Prof. Dott. A. Fieschi. Price, 8000 Lira. Pp. 718, with 83 illustrations and many charts and tables. Edizioni Minerva medica, Corso Bramante 83 (Casella postale 491), Torino 314, Italy, 1955.

The Interpretation of the Unipolar Electrocardiogram. By Gordon B. Myers, M.D. Price, $4.75. Pp. 164, with 24 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

Soap and Detergent Industry. By Oliver M. Gale. Price, $1.00. Pp. 19, with one photograph. Bellman Publishing Company, P. O. Box 172, Cambridge 38, Mass., 1955.

Report of the Sixteenth M & R Pediatric Research Conference: Retrolental Fibroplasia; Role of Oxygen. Dr. Richard L. Day, Chairman. Pp. 62, with 20 illustrations and 19 tables. M & R Laboratories, Columbus 16, Ohio, 1955.

Farmacologia: Materia medica y terapeutica. Edited by Luis E. Camponovo and Alfredo J. Bandoni. Price, not given. Pp. 644, with several photographs, 7 illustrations, and many tables and charts. Lopez & Etchegoyen, S. R. L., Junín N. 863 (R. 20), Buenos Aires, 1955.

Handbook of Toxicology: Vol. I. Acute Toxicities. Edited by William S. Spector. Price, $7.00. Pp. 408. W. B. Saunders Company, 218 West Washington Sq., Philadelphia 5, 1956.

Pathologic Physiology: Mechanisms of Disease. Edited by William A. Sodeman, M.D., F.A.C.P. Price, $13.00. Pp. 963, with 173 illustrations. W. B. Saunders Company, 218 West Washington Sq., Philadelphia 5, 1956.

BOOK REVIEWS

Surgical Physiology of Adrenal Cortex. By James D. Hardy, M.D. Price, $5.75. Pp. 191. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

In this short book the author has summarized much of the present-day knowledge concerning the role of the adrenal cortex in the metabolic response to trauma and surgery. The literature on the subject is briefly reviewed, and many of the significant contributions which Dr. Hardy has made are detailed. The material is presented in easily readable form and is well organized and carefully documented.

From a clinical viewpoint it would appear that preoperative assessment of the adrenal-corticoid response to epinephrine has little practical value, while testing with corticotropin (especially intravenously) is more rewarding in terms of predicting the postoperative course. The author has studied the metabolic response of patients to single operations, to staged operations, and to extensive burns. Patients who were subjected to three-stage thoracoplasty reacted to the second and third operation as vigorously as to the first operation. However, convalescence after the third procedure seemed somewhat more prolonged than for a single operation, as indicated by the slow return of measured physiologic activities, the most striking of which was the prolonged decrease in 17-ketosteroid excretion. The stress imposed by severe burns was characterized by unusual depression in 17-ketosteroid excretion, increased corticoid activity, and prolonged absence of circulating eosinophiles. When circulating eosinophiles remain depressed in the postburn period it may signify a poor prognosis for survival. Studies on malnourished patients with cancer show that they may exhibit diminished adrenocortical response, but there is little evidence to suggest the need for hormonal replacement therapy except in very occasional cases.

Adrenocortical hyperplasia, masculinizing adrenocortical carcinoma, and Cushing's syndrome due to hyperplasia and adrenocortical tumors are discussed in some detail.

The author states that subtotal and total adrenalectomy for essential hypertension has been carefully evaluated and appears to be of only moderate help. It must be used only in those cases in which renal failure does not complicate the clinical picture. Bilateral adrenalectomy gives some relief in about one-fifth of patients with advanced breast cancer. Such hormonal alteration is palliative and is applicable after other types of treatment have achieved their maximum effectiveness or can no longer be used. Adrenalectomy in cancer of the prostate is being investigated but seems to be of limited value.

The use of corticotropin and cortisone in surgical conditions is also briefly reviewed. These drugs are of value when given for adrenocortical insufficiency and for treatment of allergic states, certain blood dyscrasias, and the collagen diseases. These compounds have no established value in the prevention of intrapleural or intraperitoneal adhesions or in the treatment of patients with acute thermal burns or surgical infections.

The "Surgical Physiology of Adrenal Cortex" is a valuable addition to the literature on endocrinology and will be of special interest to the surgeon. It is a fitting companion to Dr. Hardy's previous book, "Fluid Therapy."

JOHN ARMES GIUS, M.D.

Poet and Psychiatrists. By Henry W. Wells. Price, $5.00. Pp. 325. Twayne Publishers, Inc., 31 Union Square West, New York 3, 1955.

A sonnet, ere the days of Merrill Moore
Was looked upon as an accomplishment—
To quarry blocks of words from mother lodes
Haul them away from where they were before
Hammer and chisel them till they were bent
Into new combinations, different modes
Then rearrange and polish, make them shine,
Garnishing fresh ideas in fresher style.
So hours and days, and sometimes weeks and years
Were spent to make one sonnet superfine.
Great poets made a few in a long while
A task so difficult it caused them tears.
This has been rectified by Merrill Moore
His day is wasted that yields not a score.

How is it that this buccaneer of sonnets
Continues almost profligate of rhyme
Since he has other full time occupations
As helping those confused, with bees and bonnets,
(And psychiatric treatment feeds on time)
By balancing depressions with elations.
For recreation, when not writing verse
He photographs the world from every angle
In number matching sonnets with his snapshots.
Great volume does not make their goodness worse.
Conchology and finding shells that spangle
A hobby that prevents reposeful nap plots.
He is a husband, father, soldier, teacher,
Physician, poet, everything but preacher.

Whence comes this energetic cavalier
Who can combine a dozen occupations
And bring to each accomplishment its grace?
The answer to his multiple career,
Achievements in a hundred combinations,
Is told by Henry Wells. He says the place
To find the cause of his fecundity
And his exuberance is in his verse.
Autobiography most clearly tells.
The South gave family, warmth and human pity,
New England sharpened without making terse
Their intertwining is described by Wells
So in the end we learn just how from Merrill—He
Writes wisely and enormously and merrily.

Veterans Administration Technical Bulletin, Ser. 10, Vol. 7, 1954. By various authors. Price, not given. Pp. 240. Veterans Administration, Washington 25, D. C., 1955.

This collection of eleven monographs is similar in format to the more famous Technical Bulletins distributed by the Armed Forces to its medical officers during World War II. All were prepared by well-qualified persons, and each of the monographs represents a thorough, but frequently not an exhaustive, discussion of its subject. Each has adequate bibliographic annotations.

Several of the monographs bring together complete analyses of specific disease entities. Thus, most of the recent advances in knowledge of leprosy are discussed by James A. Doull, while Gerald Klatskin similarly reviews leptospirosis. Another group of monographs discusses broad therapeutic principles which are pertinent to a number of diseases. In this group are a discussion of the general principles of psychotherapy by Edward A. Strecker, a discussion of dialysis in the treatment of uremia by William J. Kolff, a discourse on the pathogenesis and management of dehydration by Louis G. Welt, a review of the medical management of patients with intractable cancer by Ralph Jones Jr., and a brief discussion of the treatment of arterial hypertension by Henry A. Schroeder. Claud R. Joyner reviews the pathogenesis of coronary atherosclerosis and comments, somewhat optimistically, on the therapeutic implications of recent work. Harry B. Hudson, likewise, reviews recent advances in pathogenesis and treatment of tumors of the prostate gland. Charles E. Kossman comments on some basic principles of electrocardiography and vectorcardiography in a short article. The final article is a unique discussion of bacteremia by Ivan L. Bennett Jr.

Each of these monographs brings together a tremendous amount of material in a well-organized, concise fashion and, hence, is of particular value to the busy practitioner. The discussion by Bennett of bacteremia has unusual value, since it records a number of important practical points, many of them the result of his basic research in the study of fevers. Likewise, the concise discussion of dialysis is unusually valuable, since it contains an excellent discussion of its applications and limitations by a recognized pioneer in the field.

This book is of particular value to the internist because of the general nature of the topic, the quality of the writing, and adequate bibliographies. It is indeed unfortunate, therefore, that the bound volumes are distributed only to medical libraries, authors, and reviewers, as is mentioned in a foreword by Dr. William S. Middleton, Chief Medical Director of the Veterans Administration. Apparently, individual monographs are sent to physicians who specifically request them. Certainly these interesting and practical papers should be made available to a wide medical audience.

WALTER M. KIRKENDALL, M.D.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Vol. 46, 1954. Edited by Richard H. Hewitt, B.A., M.A., M.D.; A. B. Nevling, M.D.; John R. Miner, B.A., Sc.D.; James R. Eckman, A.B., M.A., Ph.D.; M. Katharine Smith, B.A.; Carl M. Gambill, A.B., M.D., M.P.H.; Florence Schmidt, B.S.E., and George G. Stilwell, A.B., M.D. Price, $12.50. Pp. 843, with 189 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, 1955.

The foreword for the present volume, the forty-sixth of a series, states that the material was selected with the interests of the general practitioner, the general surgeon, and the diagnostician in mind. From 629 papers published between Dec. 1, 1953, and Nov. 30, 1954, 63 are republished in full, 52 by abridgement, 20 by abstract, and 495 by title. This material is directed toward a broad audience certainly, for, as stated, "to present adequately the work of the Mayo Clinic and the Mayo Foundation" representative material of the specialties and the basic sciences is included. Subject material is presented under the broad headings of alimentary tract; genito-urinary tract; ductless glands; blood and circulating organs; dermatology; head, trunk, and extremities; thorax; brain, spinal cord, and nerves; radiology; physical medicine and rehabilitation; anesthesia, gas, and intravenous therapy, and miscellaneous. Under Miscellaneous, discussions of subjects from antibiotics to photomicrography appear. The papers are well edited and well illustrated and reflect the thoughts and efforts, either directly or indirectly, of scientifically and clinically mature persons.

The value of the volume is questioned as a reference source for the student's or the physician's library, for subject material inclusion is by chance and only a facet may be described.

The volume makes pleasant reading, and almost any medical reader will benefit from contact with this work. Within the limitation described, the volume is recommended highly.

ROBERT C. HICKEY, M.D.

Peptic Ulcer Diagnosis and Treatment. By Clifford S. Barborka, M.D., and E. Clinton Texter Jr., M.D. Price, $7.00. Pp. 290, with 33 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

The volume of literature on peptic ulcer and the recent development of many new remedies make it difficult for the practicing physician to keep up-to-date on this subject and to select the best treatment for his patients. Drs. Barborka and Texter state in the preface that their book is intended to overcome this difficulty by providing a practical concise handbook specifically for the practicing physician.

They have achieved this purpose by providing all the necessary information in a highly readable form. The short chapters, each forming a complete essay on a different aspect of peptic ulcer, will be particularly appreciated by those who have to do much of their reading in the short intervals available between other commitments. Although lengthy discussion of controversial subjects has been deliberately avoided, each chapter is accompanied by an excellent bibliography for those who wish to make a more detailed study of any particular aspect of the peptic ulcer problem. By devoting the final chapter to gastric ulcer and its relationship to cancer, the authors have succeeded in impressing the reader with the importance of this problem, and he is left with a clear summary of current opinion on management of these cases.

The appendix provides a number of suggested recipes and menus which should be of value in helping the physician to prescribe the varied and appetizing diet which the authors recognize as an important factor in helping patients maintain long-term management and in the prevention of relapses.

A point for correction in further printings or editions is that two of the illustrative x-rays have appeared upside down. The minor inconvenience of inverting the book does not, however, detract from their value as illustrations of the text.

GEORGE H. M. THORNTON, M.A., M.B., Ch.B., M.R.C.P.E.

Practitioner's Conference Held at New York Hospital-Cornell Medical Center. Edited by Claude E. Forkner, M.D. Price, not given. Pp. 411. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1955.

This book reports a series of conferences which were organized particularly for postgraduate education of the physicians in the greater New York area under the able leadership of Dr. Forkner. The subjects range through influenza and atypical pneumonia, the harmful effects of tobacco, coronary thrombosis, asthma, and a variety of other clinical problems to disorders of the feet. Dr. Forkner has chosen his panels from the talent of the whole New York area, and for the most part the contributions are interesting and instructive.

The teaching value to those present at a conference where patients and their problems are discussed by informed and nimble minds is unquestioned. On the other hand, conferences, even under able chairmanship, may degenerate into exercises in which the occasional "pearl" that may develop is lost in a plethora of loose talk and loose thinking. On p. 342 a question from Dr. Forkner as to why the panel member does not agree with the idea taught in most textbooks and in many hospitals in New York City and Boston that carbohydrates should be restricted in diabetes brings out the following reply: "I am just saying 'Don't give them concentrated sweets' because I was brought up in the school where sweets were absolutely taboo. Even though I know from experience now that they are not taboo, yet something in me holds me back, and I know it is wrong. Now that is exactly the same reason for the traditional therapy of diabetes. In Boston they have done that for 30 years, and there is no reason for changing because they think they have very good results, and I am sure that their patients do very well. They certainly do not enjoy life nor have the freedom of people who live like normal human beings, but nevertheless

they live." etc., etc. It is understandable that such irresponsible kind of talk might not have been meant by the speaker—but, if so, why publish it?

Fortunately, most of the conferences are well organized and well presented. For the internist who has a casual acquaintance with the textbook and scientific journal contributions of the teachers who participated in the Cornell conferences, the opportunity to see them at work in the clinic through these pages will prove intriguing. I was particularly impressed by the informative and straight-talking discussions of Horsfall on influenza and primary atypical pneumonia; C. P. Rhoads, Karnofsky, and Burchenal on the newer agents for cancer; John Paul and Philip Stimson on anterior poliomyelitis—though the contributions of many others are equally deserving of special mention.

Dr. Forkner is to be congratulated on having induced a distinguished group of his colleagues to put together such an instructive group of conferences, and his own direction of the discussions played no small part in their success.

PAUL S. RHOADS, M.D.

Cardiac Auscultation: Including Audio-Visual Principles. By J. Scott Butterworth, M.D.; Maurice R. Chassin, M.D., and Robert McGrath, M.D. Price, $4.50. Pp. 111, with 54 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

The authors of this book are justifiably recognized for their development and popularization of equipment for the combined audiovisual study of cardiac auscultation. No one familiar with this equipment can fail to appreciate the impact of simultaneously seeing what one hears through the stethoscope. This book is the outgrowth of their experience in teaching clinical auscultation by this method.

The book contains much of the standard information expected from any discussion of the subject. However, the departures are praiseworthy.

Most textbooks in physical diagnosis outline the physical principles of sound either so superficially or so complexely that the average student soon loses interest in incorporating this basic information into his everyday and life-long analysis of cardiac auscultation. The discussion in this book is concise, clear, and meaningful. The classfication of murmurs simply as pathologic and nonpathologic is especially commendable. The majority of the more than fifty illustrations are faithfully reproduced stethograms. Portable audiovisual equipment is described which is practical for use by individuals and small groups. The sound recordings from which the stethographic illustrations in the book were made are available and when combined with the study of the book provide a lasting educational experience. Even without the sound recordings, the book has special merit. Physicians, teachers, and medical students alike will benefit from this fresh approach to a subject basic to the practice of medicine.

L. E. JANUARY, M.D.

New
Evidence
on

Rauwiloid

confirms and defines its advantages in the treatment of HYPERTENSION

- Rauwiloid represents the balanced, mutually potentiated actions[1] of several Rauwolfia alkaloids, of which reserpine and the equally antihypertensive rescinnamine have been isolated.
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1. Cronheim, G., and Toekes, I. M.: Comparison of Sedative Properties of Single Alkaloids of Rauwolfia and Their Mixtures, Meet. Am. Soc. Pharmacol. & Exper. Therap., Iowa City, Iowa, Sept. 5, 1955.

2. Moyer, J. H.; Dennis, E., and Ford, R.: Drug Therapy (Rauwolfia) of Hypertension. II. A Comparative Study of Different Extracts of Rauwolfia When Each Is Used Alone (Orally) for Therapy of Ambulatory Patients with Hypertension, A.M.A. Arch. Int. Med. *96*:530 (Oct.) 1955.

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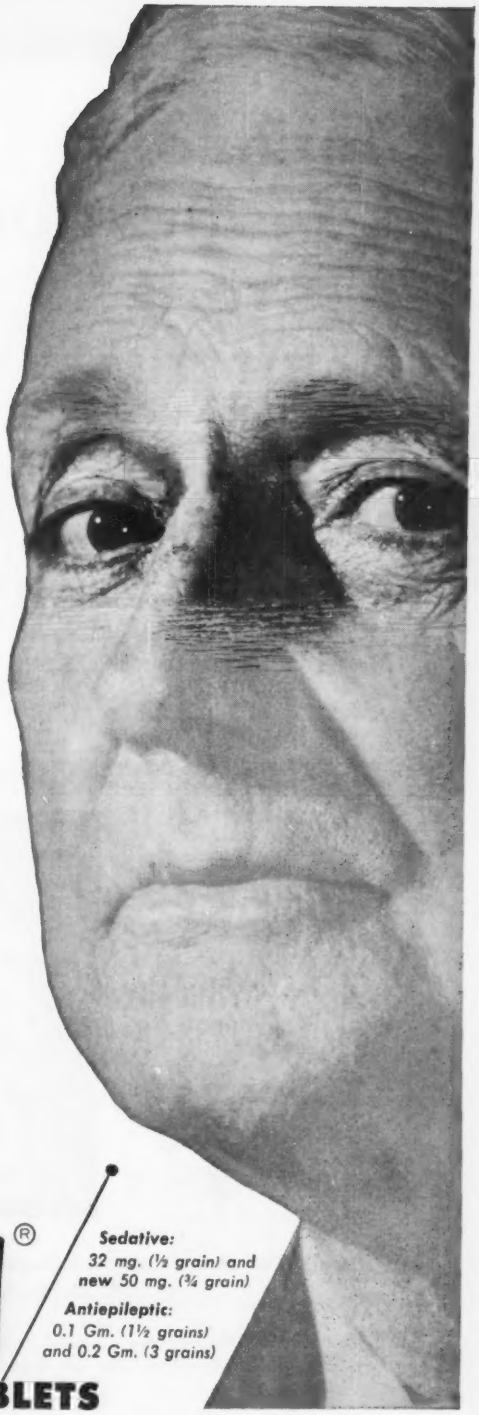

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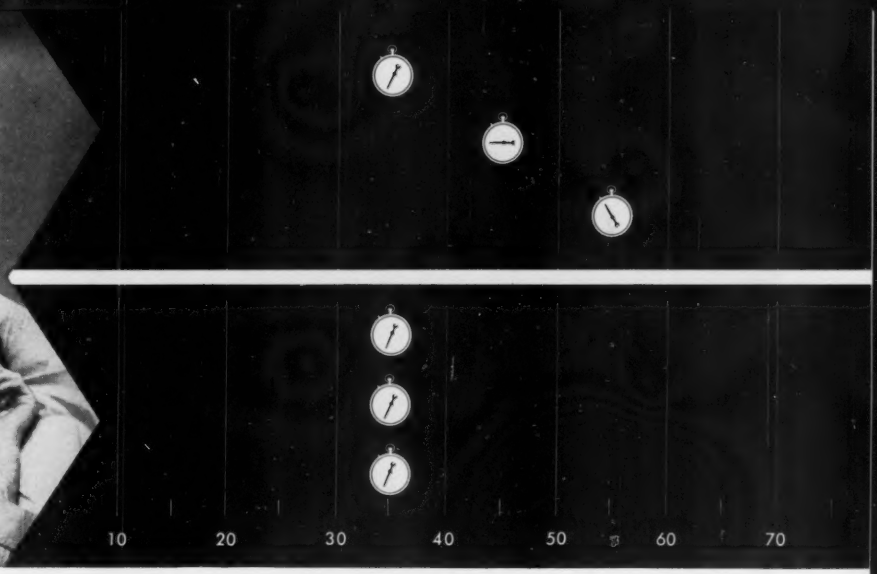

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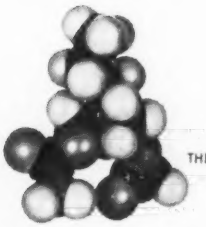

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